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CATALEPSY

AN EXPERIMENTAL STUDY

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A somnolent state, characterized by loss of voluntary motion and sensibility, and a peculiar plasticity of the muscles are the cardinal features of catalepsy. The plastic condition of the muscles makes it possible to mold the limbs and body into odd postures which can be retained for long periods. Experiments on cats in which these symptoms have been produced by lesions at the base of the brain in the region of transition between the forebrain and the midbrain have shown that there is no binding relationship between the depth of the somnolence and the ease with which the animals can be made to assume and maintain unusual postures. In the monkey we have found it easy to produce somnolence but not true catalepsy. On the other hand, plasticity is easily produced in cats, but in these animals it is extremely difficult to tell whether the immobility and posturing are accompanied by somnolence. During the days immediately following the placing of the lesions in the brain our cats seemed clearly to be asleep. However, many of these animals could be posed in peculiar postures for many days after they had ceased to be particularly drowsy. The observations to be reported in this paper are concerned chiefly with the muscular plasticity seen in these animals. The question of somnolence is being studied more in detail in another series of experiments which is being carried out on monkeys.

In attempting to study the possible significance of the area immediately rostral to the red nuclei, we placed lesions in the region between the mamillary bodies and the third nerves bilaterally and close to the midline in cats. The most striking result in some of these animals was the immediate onset of a state in which inertia, lethargy and plastic hypertonus of the muscles combined to produce a picture of catalepsy.

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A brief report of a number of these early experiments was made at the time.[1] It was soon noted that this condition greatly resembled the catalepsy caused by bulbocapnine, and investigation showed that cats with lesions in the retromamillary area were much more susceptible to the action of the drug than normal cats.[2] Records of observations on a large number of cats in which such lesions were produced have accumulated, and a summary of these detailed studies is herewith presented.

METHODS

The lesions were produced by use of the Horsley-Clarke stereotaxic instrument, the use of which has been described elsewhere.[3] Both bipolar and unipolar needle electrodes have been used, but it is believed that the unipolar type produces the most satisfactory lesions with a minimum of damage incidental to the insertion of the needle. Three small lesions were placed close together in a line rostrocaudally and 1.5 mm. from the midline, close to the ventral surface of the brain in the region extending from the posterior hypothalamic nucleus to the oculomotor nerves. Lesions thus placed are ordinarily confluent, forming a single elongate lesion which, when duplicated on the opposite side of the midline, is associated with the aforementioned symptom complex.

The operations for the so-called acute experiments were performed with the cats under ether anesthesia; the animals were observed for twenty-four hours after recovery from the anesthesia and then killed. In the so-called chronic experiments the cats were anesthetized with pentobarbital sodium and the operations performed under carefully maintained aseptic conditions. The animals usually required considerable nursing, including tube feeding and cleaning.

At the end of the period of observation the cats were killed by bleeding; the heads were perfused with a dilute solution of formaldehyde U.S.P. (1:10), and the brains were removed. The upper portion of the brain stem was sectioned, and alternating sections were stained with cresyl violet and by Weil's method.

Special methods involved in certain aspects of the experiments will be referred to in the text.

OBSERVATIONS

A total of fifty-five cats have shown catalepsy of varying duration following damage to the ventral part of the brain stem from the posterior portion of the hypothalamus to the third nerve. In seven the period of survival was short—they were subjected to the so-called acute experiments—and five of these were dealt with in the previous paper. The remaining forty-eight cats were subjects of chronic experiments. These animals may be divided into two categories: those in which the plasticity endured for less than seven days and those in which it lasted seven days or more. In the first category there were thirty-one cats, of which thirteen died or were killed within the seven day period. In

1. Ranson, S. W., and Ingram, W. R.: Catalepsy Caused by Lesions Between the Mamillary Bodies and Third Nerve in the Cat, Am. J. Physiol. **101**:690, 1932.

2. Ingram, W. R., and Ranson, S. W.: Bulbocapnine: Effect on Animals with Lesions of the Central Nervous System, Arch. Neurol. & Psychiat. **31**:987 (May) 1934.

3. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotaxic Instrument, Psychiat. en neurol. bl. **38**:534, 1934.

the second category there were seventeen animals, of which nine died or were killed within thirty days of the operation; in five of the remaining eight the plasticity persisted for more than thirty days. Table 1 indicates the degree and duration of this symptom and the period of survival of each cat subjected to the chronic experiment.

TABLE 1.—*Data on Cataleptic Cats*

Cat	State of Catalepsy	Duration of Plasticity	Period of Survival	Manner of Death
3	Poor	10 mos.	10 mos.	Killed
4	Fair	4 days	10 mos.	Killed
5	Fair	2 mos.	2 mos.	Killed
6	Good	4 days	4 days	Killed
7	Fairly good	20 days	20 days	Killed
8	Good	9 days	9 days	Natural
9	Good	9 mos.	9 mos.	Killed
10	Good	6 days	6 days	Killed
11	Fairly good	4 days	4½ mos.	Killed
12	Poor	24 days	3½ mos.	Killed
15	Fair	13 days	3¼ mos.	Killed
18	Fairly good	8 days	3 mos.	Killed
21	Good	10 days	3 mos.	Killed
22	Fairly good	6 days	6 days	Natural
23	Good	5-6 days	6 days	Natural
24	Marked	7 days	7 days	Accidental
47	Good	9 days	9 days	Natural
50	Fairly good	6 days	1 mo.	Killed
52	Marked	4 mos.	4 mos.	Killed
53	Fair	3 days	3 wks.	Killed
54	Fairly good	20 days	20 days	Killed
55	Fairly good	8 days	8 days	Natural
138	Poor	6 days	15 days	Natural
140	Fair	4 days	4 days	Natural
142	Fair	4 days	4 days	Natural
143	Good	5 days	8 days	Natural
146	Good	5 days	5 mos.	Killed
147	Fair	6 days	6 days	Natural
148	Good-fair	5 days	5 mos.	Killed
149	Fair	5 days	8 days	Natural
154	Fair	3 days	6 mos.	Killed
155	Fairly good	5 days	6 mos.	Killed
263	Good	8 days	8 days	Natural
266	Fair	4 days	15 days	Killed
268	Fairly good	4 days	14 days	Killed
276	Traces	2 days	9 days	Killed
277	Poor	11 days	11 days	Killed
278	Fairly good	6 days	6 days	Natural
283	Good for 7 days fairly good for 30 days	37 days	50 days	Killed
284	Good	6 days	36 days	Killed
285	Fairly good	6 days	6 days	Natural
286	Fairly good	5 days	5 days	Natural
287	Fair	5 days	5 days	Natural
288	Good	4 days	4 days	Killed
289	?	3 days	3 days	Natural
291	Marked	41 days	41 days	Killed
294	Good	7 days	7 days	Killed
295	Fair	4 days	21 days	Killed

The pathologic findings in cases of short duration are likely to prove misleading, since in these the effects observed may have been due to edema, pressure or irritation of structures not included in the damaged area. Such cases will not be considered in detail here. Since it is obviously impossible to describe the behavior of each animal in the series, a small group of cats representative of the various degrees of involvement has been chosen, and fairly detailed summaries of the findings in these animals will be presented. Seven animals are included: cat 283, which showed good plasticity for seven days and fairly good

plasticity for thirty days; cat 291, which showed marked plasticity for forty-one days; cat 5, which displayed fair plasticity for two months; cat 7, which posed fairly well for nineteen days; cat 9, which could be made to assume and maintain odd postures as long as nine months after the operation; cat 52, which showed marked plasticity until it was killed at the end of four months, and cat 54, in which the plasticity was fairly good for eighteen days. The periods of survival of these animals are shown in table 1.

THE GENERAL BEHAVIOR OF CATS WITH DELAYED RECOVERY

In its early stages the catalepsy resembles that observed in animals subjected to acute experiments. There is profound somnolence, loss of motor initiative and a remarkable plastic hypertonus of the muscles. The animals can be aroused from sleep, and a limited amount of activity can be induced. This is chiefly confined to protective or righting movements: thus, when such a cat is pushed from the edge of a table it may gather itself together and leap so as to strike the floor right side up on its feet. Ordinarily, however, the animals remain in statuesque positions for hours and, because of the plasticity of their muscles, may be molded into various poses, some of which are bizarre. This amenity to passively induced poses was studied in a routine manner, certain attitudes being especially suitable, for example, a position in which the forelimbs were folded under the chest but with the hindlimbs extended, the "praying pose," a position in which the cat stood with the forelimbs widely abducted in the "spread" position, one in which the forelimbs were placed on an elevated support and one in which the animal clung with the forepaws to a horizontal bar and thus supported the weight of the body in the "hanging" position (fig. 1). A "bridging" position, in which the cat was placed with the forelimbs and hindlimbs on separated supports, the trunk hanging free, could sometimes be induced. The tendency to retain such passively induced postures persisted for varying periods and certain animals could still be posed months after operation.

It will be seen from the report of specific experiments which follows that there is usually a prompt onset of lethargy and somnolence. Exceptions to this may occur, as shown by cat 9, in which catalepsy developed rather gradually during a stage marked by irritability and bad temper. There can be no doubt, however, that somnolence is an important constituent of the early stages of this syndrome. This sleep is of distinctly pathologic variety and may persist under conditions which would cause prompt activity in a normal cat. Strong stimuli are required to arouse these animals at this stage, and the period of wakefulness is rather short. It should be noted that the somnolence was not permanent but disappeared after varying periods. This makes

it necessary to modify the opinion, expressed in the first paper,[1] that the readiness to assume unusual postures was directly related to the sleeping state, for cats 9 and 52 remained willing to pose at times when they seemed quite conscious and long after the stage of somnolence had passed.

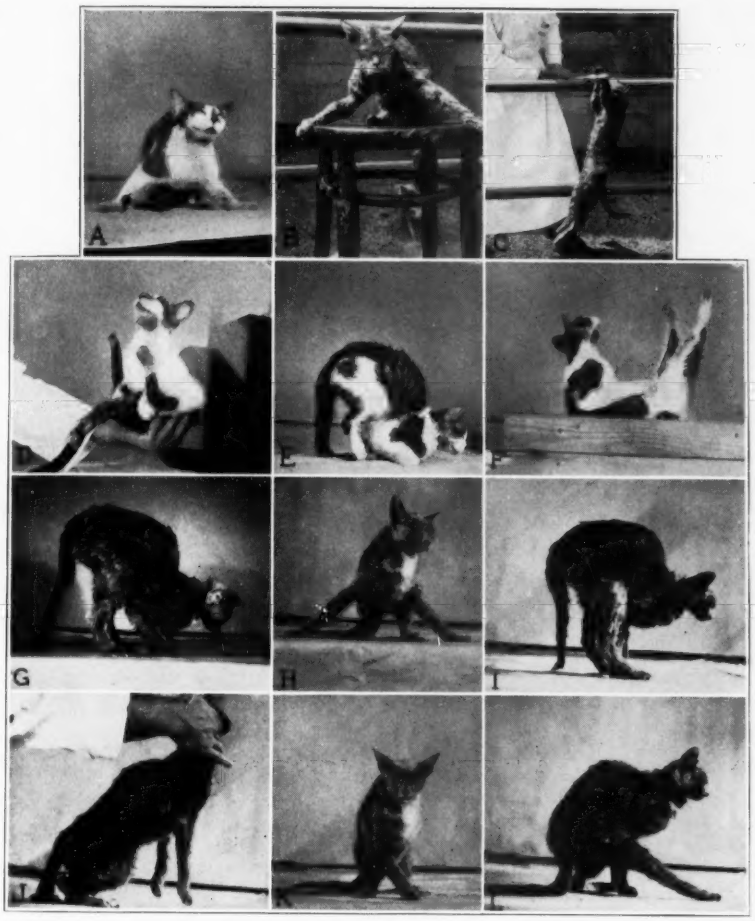


Fig. 1.—Photographs of cataleptic cats, showing some of the passively induced postures which the animals maintained for considerable periods of time. The animals were indifferent to their condition and suffered no pain or discomfort. *A, D, E* and *F* show cat 7 fourteen days after placing of the lesions shown in figures 14 to 17; *B* and *C* show cat 52 thirty-three days after the placing of the lesions shown in figures 22 to 25; *G, H, I, J, K* and *L* show cat 9 twenty-one days after the placing of the lesions shown in figures 18 to 21.

The behavior of the cats in the later stages was especially interesting. After the period of somnolence a marked poverty of movement

persisted. The animals would sit upright in one spot for hours, almost motionless, with an unchanging vacuous stare and only occasional slight shifts of position. Those with complete paralysis of the oculomotor nerve usually kept their eyes closed, although they were known to be awake, since they greeted the observer with cries when he entered the room at feeding time. The tendency to pose varied in different animals, and was more pronounced at certain times than at others. Odd attitudes were frequently assumed spontaneously. The more mildly affected cats sometimes moved about a little, usually in an aimless fashion. It was difficult to cause the cats with severe catalepsy to move at all. For example, on the few occasions when it was possible to coax cat 9 to walk a few steps the animal was usually on edge with hunger, and the sight of food some distance away was the only adequate incentive. The slow hesitating gait, which is described in the report of the experiments, resembled nothing seen by us in a fairly wide experience with cats. In cat 52 movement was obtained only when the animal was under the influence of cocaine and consisted of an endless strutting in brief circles.

During the first days and weeks after operation the cats showed no interest in food and required feeding by tube. After the somnolent stage was passed they began to indicate hunger by cries and apparent restlessness. However, even though hungry they rarely ate if left to their own devices. It was necessary to give milk by stomach tube or by introducing the fluid into the mouth from a bottle. Meat was taken only when held to the lips, and often only when forced into the mouth. Once the food was in the mouth there seemed to be no more difficulty; it was masticated and swallowed readily and even voraciously. Thus there was no true dysphagia, except possibly in one case (cat 5) in which the meat was not swallowed even when placed in the mouth.

In the initial stages all the cats showed increased tonus of the extensor muscles. *Stütz* reflexes were readily elicited, and there was manifest resistance to passive flexion of the limbs. This phase of the study will be dealt with in a subsequent section. For the present it is sufficient to say that the strength of the tonus reactions diminished rapidly and disappeared after a time. In occasional cases there was hypertonicity of the extensor muscles of the neck, which produced a mild opisthotonos that persisted even when the animal was placed on its back. A particularly striking and almost uniform phenomenon was increased tonus of the flexor muscles of the neck and trunk, including those of the abdominal wall, when the animal was placed on its back in a trough. Under such circumstances the spinal column was flexed and the head and pelvis were raised, and in certain cases the flexion was so extreme that the animal was curled up into a ball, the hindfeet over the head

and the forepaws clutching the hindlimbs. On the other hand, when the spine was passively extended these animals lay flat on their backs, illustrating well the plasticity of the muscles.

It was difficult to determine the mental condition of such relatively unresponsive beasts. The chief evidence that this was decidedly abnormal rests on observation of cats which after the plasticity of the muscles had disappeared continued to behave in an abnormal manner. However, one could not work long with the cats with marked chronic catalepsy without receiving the impression that they were quite conscious and receptive. Certainly they learned to recognize the attendant who fed them, and they expressed this recognition after a fashion. They responded somewhat to petting, but it was usually difficult to arouse them emotionally by painful stimulation. Examples of loss of emotional expression may be found in the report of the specific experiments. This stolidity was not always present from the beginning, however. In several animals the postoperative period of recovery was marked by the onset of violent rage on slight disturbance; in others there were spells of milder irritability, which passed off after a few days, changing to a profound calm. The calm attitude was not free from surprising reactions, however, for a cat which showed practically no agitation in the presence of barking dogs was seen to strike at another cat which approached too closely.

To recapitulate, in favorable instances lesions involving the caudal part of the hypothalamus and the upper part of the mesencephalic tegmentum may produce a syndrome characterized by initial somnolence, persistent loss of motor initiative, marked disinclination to walk, acceptance of passively induced poses, indisposition to eat even when hungry and vacuity of expression. Ability to carry out righting reactions and to adjust the position of the body in a protective manner was retained. There was strong suppression of emotional reactions in many cases. After recovery from the initial somnolence, consciousness was retained, and there was a fair degree of mental alertness.

Six of the animals were tested by Dr. L. J. Pollock to determine what changes in the curves for respiratory movements, as recorded on a kymograph, followed stimuli of various kinds. His observations have been summarized by him as follows:

> When the animals were quite somnolent no critical change in the form or frequency of respiration was noted after such stimuli as the vibration of a tuning fork, a loud drumming noise, strong light, as from a 1,000 watt lamp, pressure on the extremities or blowing on the face or ear. There regularly occurred a marked change in response to olfactory stimulation produced by cloves, smoke, pyridine or chloroform. Pricking of the leg was accompanied by a response of lesser degree. Often after an olfactory or painful stimulus had been applied the animal became partly aroused and then responded, with a slight irregularity of

rhythm or extent of respiratory movements, to loud noise, to touching the head and extremities, to the sound of a tuning fork, to blowing on the face and even to a threatening movement of the hand.

When the animals were not so deeply asleep but were in a state of immobility, usually one could not observe any voluntary response to the aforementioned stimuli. The curve for respiratory movements, however, showed changes resulting from all the stimuli, and the changes were most marked in the case of olfactory and painful stimuli. On one occasion a cat was brought near the animal being studied and made to spit or snarl by pinching its tail. The cataleptic animal showed no visible reaction, but the respiratory wave became irregular. This is similar to the condition seen in patients with catatonic dementia praecox, in whom no voluntary reaction to stimuli can be observed but an involuntary response expressed in respiratory arrhythmia occurs.

REPORT OF SPECIFIC EXPERIMENTS

CAT 283.—Operation was performed on June 6, 1932, and the animal was killed on July 26, 1932. The lesions are illustrated in figures 2 to 5.

The day after operation the cat was somewhat weak, showed unsteadiness and a tendency to circle left in walking and posed for short periods. There was a distinct impression of drowsiness. There were flexion of the trunk and fair plasticity of the limbs when the animal was supine. Sleepiness persisted for several days; spontaneous movements were rare; the eyes were usually closed, and various poses, including the praying position, could be induced. There was no significant rigidity of the limbs when the cat was suspended with the limbs hanging free. By the fifth day the animal was more easily aroused from its lethargic state but would not move about spontaneously. The forced movement was now reversed, so that the head was turned to the right. There was good acceptance of poses. When the animal was supine, an evident flexor tonus of the forelimbs was noted, the hindlimbs showed slightly increased extensor tone and there was moderate plasticity of all the limbs. The cat paid no attention to food and was sustained by injections of dextrose.

On the seventh day the somnolence was less evident, and there was more spontaneous activity. Various poses could be induced, and though the animal was able to walk it was unwilling to do so. It remained in one statuesque position for as long as an hour, looking about stupidly. This condition persisted for a long time, with gradual increase in the amount of spontaneous movement, while there was some diminution in the maintenance of passively induced poses. In walking the animal showed a slight overstepping with the right forelimb and a tendency to circle to the right. The general behavior was stupid. When coaxed, the cat could be induced to eat meat placed in its mouth; the movements of eating were well performed. Milk was fed by tube for over a month. Occasionally there was a relapse into a profound state of catalepsy. There was good reaction to painful stimuli at times; at others it was difficult to arouse the cat. Occasionally the animal was seen to salivate profusely when handled. When subjected to an unusual exigency the protective movements elicited were well carried out. Sometimes loud, sudden noises produced cringing and cowering.

About five weeks after operation a live rat was placed before the cat. The latter responded with amazing speed, clutching the rat's neck with the jaws. The rat was not killed at once, however; the cat stood holding it for about seven minutes, until it was choked to death, carried it about, walking with the usual dilatory, intermittent gait, for approximately ten minutes, then dropped it and thereafter ignored it completely. This performance was repeated when another

rat was offered. When the cat was confronted with barking dogs, the reactions were in a sense normal—the animal hissed, lashed the tail and struck out with the forepaws, but there was little if any pilomotor activity.

On July 21, at the suggestion of Dr. Pollock, the cat was given 0.25 grain (0.016 Gm.) of pentobarbital sodium intramuscularly, but when the animal emerged from the anesthesia no change from the usual behavior was noted. On July 22 the animal was sedentary, the stupid attitude being maintained. Few poses could be induced. When the cat was supine the trunk was flexed, and there was some plasticity of the limbs. There was no significant rigidity when the cat was suspended. On July 26, under Dr. Pollock's direction, Dr. Boshes transfused blood from this animal into a normal cat, but no noteworthy effects were observed in the latter. The cat was then killed.

CAT 291.—Operation was performed on June 17, 1932, and the animal was killed on July 28, 1932. The lesions are illustrated in figures 6 to 9.

On the first day after operation the cat was found asleep in a peculiar position, with the head and neck drawn backward. It was unable to stand and showed a marked twist of the head, so that the left ear was held lower than the right. When suspended in a hammock, fair positive *Stütz* reactions and marked resistance to passive flexion were observed in the forelimbs; in the hindlimbs these reactions were slight. On the following day the opisthotonos had disappeared, and while the forced movement was maintained the animal could stand and was amenable to induced poses, including the praying position. When the animal was supine there was flexion of the trunk and good plasticity of the limbs. There were fair *Stütz* reactions when the cat was suspended. At this time the animal took some food voluntarily, but subsequently it was necessary to feed it by tube.

For several days thereafter the cat showed some irritability, reacting to handling by growling and hissing aimlessly, although in general it was remarkably somnolent and when undisturbed sank into a deep slumber resembling normal sleep. The senseless irritability cropped out from time to time during the next month. The forced movement diminished but persisted in some degree throughout the life of the animal. On the third day the catalepsy was marked; there was good posing, and when the cat was supine there was considerable rigidity of the limbs as well as good plasticity. During the days which followed the tonus reactions diminished greatly, but the somnolence persisted. The acceptance of passively induced poses was remarkable. The right pupil was dilated and fixed. Although the animal was able to walk, it was unwilling to do so and remained sitting or standing in one spot for hours in stiff statuesque positions, often apparently asleep. About two weeks after operation a frequent spontaneously assumed and maintained attitude was one in which the cat stood with the back arched and the left hindfoot raised and extended forward beneath the chin, as if it had been frozen when about to scratch itself. At this time it was noticed that there was considerable pilomotor activity on the least handling. In general, sensation appeared to be normal. Good health was maintained except for vaginitis which lasted about two weeks.

A considerable rigidity of the muscles of the neck was a noteworthy feature in this cat. When the animal was placed on its back the pelvis was raised and the trunk flexed; the neck, however, remained extended although the head was supported clear of the floor. At times a sort of waxy flexibility of the neck was observed.

On July 12, twenty-five days after operation, the remarkable somnolence and immobility were still retained. The cat did not eat voluntarily but swallowed meat placed in its mouth with apparent avidity. When confronted with barking dogs it hissed and lashed its tail but made no effort to escape; at this time there

was little pilomotor activity, but when the animal was handled under other circumstances there was marked erection of the hair. When it was supine there was no *Stütz* reflex, and resistance to passive flexion was not greater than normal. There was fairly good plasticity of the forelimbs in either the flexed or the extended position. The hindlimbs showed considerable tonus of the flexor muscles.

On July 27 the behavior was essentially unchanged. Two days later the animal was killed by transfusing its blood into a normal cat. Dr. Boshes, who made the transfusion at Dr. Pollock's suggestion, observed no effect on the behavior of the normal cat.

Cat 5.—Operation was performed on Sept. 14, 1932, and the animal was killed on Nov. 11, 1932. The lesions are illustrated in figures 10 to 13.

The day after operation, cat 5 was found asleep and seemed very stupid when aroused. The body-righting reactions were intact. Passively induced poses were rather well maintained. When the cat was supine, the trunk was flexed, the forelimbs were flexed and adducted and the hindlimbs were extended. When it was suspended fair positive *Stütz* reactions were obtainable. The next day these reactions were greatly diminished. This general condition lasted for several days, during which a slight forced curvature to the left developed. The animal was quiet and indifferent when handled. There was little inclination to walk. Odd attitudes were assumed spontaneously, but maintenance of passively induced poses was relatively brief. A trace of rigidity and plasticity persisted in the hindlimbs. The cat was often found in a sort of half standing, half sitting position, staring straight ahead with a vacuous expression. Little or no attention was paid to sharp sounds. Tube feeding was necessary. A general attitude of stupidity and lethargy became characteristic.

The tendency to assume induced poses diminished somewhat as time went on. Periods of quiet were occasionally varied by intervals during which the animal was relatively restless. The plasticity of the forelimbs when the cat was supine became reduced; that of the hindlimbs was well maintained. When the cat was in this position, movements of the head and what seemed to be coarse tremors of the limbs were noticeable. During the fourth week, when a rat was freed the cat merely watched it in a bewildered manner.

On October 17 it was still necessary to feed a liquid diet by tube; meat was refused. Spontaneous statuesque poses were maintained for long periods, but passively induced poses were not held long. When placed before a group of barking dogs the cat pricked up its ears and looked mildly interested but showed no other signs of emotion. This condition remained in general rather stationary for a long time, but finally a physical decline became evident. On November 11 the animal was weak and unable to stand. Pain stimuli were disregarded. The animal had never eaten voluntarily since operation and had been fed milk, with the occasional addition of a little ferric ammonium citrate, by tube. Apparently it was dying of starvation; it was killed.

Cat 7.—Operation was performed on Sept. 16, 1932, and the animal was killed on Oct. 6, 1932. The lesions are illustrated in figures 14 to 17.

The animal was profoundly somnolent for forty-eight hours after the operation. On the third day it was sleepy and amenable to all sorts of induced poses. There was a forced movement to the left. When the cat was supine the trunk was flexed and there was fair rigidity and plasticity of the limbs. When suspended it showed a fair amount of tonus of the extensor muscles of the limbs. During the next few days the somnolence continued, but considerable irritability was displayed, and the animal occasionally exhibited a blind rage when handled. There

was marked ataxia in walking. Various poses, including the praying attitude, could be induced. Eight days after operation the hyperirritability largely disappeared, and much more activity was shown; the cat moved about with a steppage gait. The *Stütz* reactions had disappeared. A characteristic attitude during the subsequent days was squatting with the head tilted back, and the animal apparently slept in this position. Some induced poses were maintained for a time. It was necessary to feed the cat by tube. A generally stupid behavior, with only occasional spontaneous movements, persisted until it was killed.

On October 3 the remarkable retraction of the neck and elevation of the chin were still noticeable. No interest was shown when a rat crawled over the cat's back. It made no effort to keep itself clean. Somnolence was still evident, and induced poses were accepted. Increasing weakness and emaciation made it necessary to kill this animal on October 6.

CAT 9.—Operation was performed on Sept. 23, 1932, and the animal was killed on June 14, 1933. The lesions are illustrated in figures 18 to 21.

The first day after operation this cat was irritable and resented handling. The body-righting reactions were present. The pupils were well dilated. There was considerable resistance to *Stütz* stimulation in the forelimbs and less in the hindlimbs. On the third day the chief characteristics were hyperirritability, remarkable flexor tonus in the hindlimbs and a forced movement in which the head was turned to the right. A tendency to somnolence developed during the first week, although the irritability persisted during this time. When the cat was supine there was an impression of marked spasticity of the hindlimbs and fairly good plasticity of all the limbs. On October 3 various induced poses were accepted, including the praying position. The cat's disposition had changed remarkably, and it now purred when handled. It usually sat in one place, with the head thrown well back, and slight movements of the limbs could be seen. When it was supine the trunk was flexed; the *Stütz* reactions were absent, and plasticity of the limbs was only fair. It was necessary to feed the animal by tube. The left pupil was dilated and the right constricted. The cataleptic state seemed to be progressive.

On October 15, the twenty-second day, the cat was found lying on its side with the limbs curled up clear of the floor. Induced poses were accepted and well maintained, and the animal could be balanced on the palm of one's hand as shown in figure 1 *D*. When the animal was standing the limbs seemed well extended and the feet were placed close together, with the back arched. The axial muscles were so rigid that the whole body could be raised by a finger placed under the cat's chin (fig. 1 *J*). When the cat was supine the *Stütz* reactions were minimal, but there were noticeable spasticity of the limbs and coarse tremor-like movements. When it was suspended there was strong resistance to passive movement of the forelimbs. During this period the temperature was rather low—from 96 to 100 F. The animal was remarkably sedentary and lacked motor initiative. No attention was given to mice. When placed before barking dogs the cat showed no interest, and only when held against the screen of the dog's cage did it arouse itself enough to hiss and strike. There was no erection of the hair or lashing of the tail.

There was no noticeable change in behavior for many months. The cat was fed milk by tube and ate meat placed in its mouth. It eventually learned to lap milk from the end of a tube.

In March the cat was seen to stand for long periods with the limbs crossed or with one of them raised in an odd posture. When one picked it up an impression of great muscular rigidity was received. It would sometimes strike at other cats which approached too closely. General health remained good, and it appeared to

enjoy being petted. It made no attempt to keep itself clean. In many respects its behavior resembled that of a decorticate animal. Rarely the cat could be persuaded to walk—the gait was extremely slow and hesitating, apparently requiring great effort; a low center of gravity was maintained, and the movements of the limbs were "stiff." A limb was lifted and poised for a short time before being moved forward or down, and sometimes the hindlimbs were shaken after being lifted. In the ordinary sessile condition the cat gave the impression of rigidity, and little, almost imperceptible, movement could be seen.

On June 14 the animal's condition suddenly changed; it became weak and was prostrated, although the behavior had been as usual until the evening of June 13. The temperature dropped below 94 F. When the cat lay on its side there seemed to be a slight opisthotonos; the forelimbs were extended and resisted passive movement. The animal was killed at this time. No cause for the sudden collapse was found; except that the mucosa of the colon was inflamed and filled with minute hemorrhagic areas, no morbid features were found at autopsy.

CAT 52.—Operation was performed on March 27, 1933, and the animal was killed on July 29, 1933. The lesions are illustrated in figures 22 to 25.

This animal showed fairly good plasticity on the day after operation. The body-righting reactions were apparently intact. Passively induced poses were accepted and fairly well maintained. Both pupils were widely dilated. When the cat was supine there was flexion of the trunk; increased tonus of the extensor muscles of the limbs and good plasticity were evident. The cat was quite irritable during the first few days. A pronounced somnolence was noted, and as the animal's general physical condition improved the maintenance of induced poses became striking. When the animal was at rest a marked tendency to flexion of the limbs and spine was exhibited. During the first three weeks the temperature was low (from 96 to 97 F.), but it returned to normal by April 19. Tube feeding was necessary throughout the remainder of the cat's life.

The plasticity of the muscles persisted in about the same degree for about four months, although the *Stütz* reactions diminished in time. The disposition to maintain induced postures was marked, and the cat would hang clear off the ground, the forepaws clutching a rod, for some time. During the first month the somnolence gradually diminished, but the capacity for spontaneous movement never returned, although peculiar attitudes were sometimes voluntarily assumed.

The marked plasticity and sedentary behavior were still present in June. The limbs were stiff, and the rigidity was most evident when the cat was supported by a hand placed under the belly. When unduly aroused the animal responded by crying and expressed emotion by growling and hissing. On June 15 a total of 15 mg. of cocaine was administered in two injections. The stimulatory effects were rather marked. Within a few minutes there seemed to be a brighter, more alert expression of the face and increased movement of the limbs. Induced poses were refused, and the righting reactions were executed more promptly than usual. The cat became obviously excited, turning round and round, with very short steps, lifting the feet and replacing them in a hesitant manner. No true progress was made. There was some incoordination of the hindlimbs. The head was moved back and forth aimlessly. There was frequent licking of the nose and lips. After about an hour this excited state began to subside, and by the following day the animal had reverted to its usual condition.

On July 28 the cat was found to exhibit the same behavior as before. It was well nourished, although it had been tube fed from the beginning. It had developed the ability to seek fleas in easily accessible parts of the body. The placing reactions

seemed absent. The cat could adjust itself to certain exigencies; for instance, when pushed from the edge of the table it jumped and lighted well. On July 29 the cat was killed.

CAT 54.—Operation was performed on March 31, 1933, and the animal was killed on April 20, 1933. The lesions are illustrated in figures 26 to 29.

At the beginning this animal showed marked catalepsy, which receded somewhat during the eighteen days' survival. On the day after operation there was good acceptance of passively induced poses. An odd, crouching position was ordinarily assumed, but the cat could be made to walk a few steps. Marked drowsiness was noted for a number of days. When the animal was supine the trunk was flexed, and increased rigidity and plasticity of the limbs were noted. Good *Stütz* reactions were elicited when the animal was suspended. The left pupil was dilated; the right was normal. The body-righting reactions were present, but initiative for further movement seemed largely lacking. By the sixth day a characteristic attitude was that of standing with the head lowered. Posing was good. Feeding by tube was necessary part of the time. The hypertonus of the extensor muscles diminished as time passed, and by the seventeenth day fair *Stütz* reactions could be elicited from the hindlimbs only, although there was surprising plasticity of the limbs. At this time more spontaneous activity was shown. One received an impression that the limbs were stiff and awkward, stiffness being especially evident when the cat was held suspended by a hand placed under the belly. Acceptance of poses was limited. Occasionally, however, a spontaneously assumed posture was retained for a considerable time. Walking was hesitant, the forelimbs showing considerable adduction. Occasionally the animal was seen to stop in full stride and "freeze" into a statuesque position. At this time a severe infection of the respiratory tract developed, and on April 20 the cat was killed.

GENERAL BEHAVIOR OF CATS WITH TRANSIENT CATALEPSY

In eighteen cats which had more or less extended survival periods the plasticity lasted less than seven days. There were also thirteen cats which died within the seven day period. In all, the initial symptoms were typical, but the later behavior deserves brief comment. The rapidity with which recovery from the cataleptic state took place varied; in some cases it was sudden, the symptoms disappearing overnight; in others several days was required for complete recovery. Although the behavior of some of these animals became fairly normal, it is doubtful whether they completely regained their former status, and many of the others continued to behave peculiarly. In general, they were less active than normal cats, and some showed periods in which they sat motionless for hours, with only occasional spells of activity. They were usually able to feed themselves, but sometimes they had to be coaxed to take food. They were usually calm and unemotional and showed little interest in their surroundings. Habits of cleanliness were often reacquired. Certain animals regained normal locomotion; others showed disorders of movement incident to injury of the tegmentum: various degrees of dysmetria and ataxia were observed, and forced movements were not uncommon. Normal sexual behavior was noted

in some cases—a number of females became pregnant and bore young in the postcataleptic state; others showed no signs of eroticism.

There may be a correlation between the degree of behavior abnormality in cats in the postcataleptic state and the depth and duration of the catalepsy. Thus in cat 12, which showed a poor sort of catalepsy for only two days, there was merely a motor disturbance, while cat 15, in which the catalepsy was fairly good and plasticity lasted thirteen days, behaved peculiarly thereafter.

It should be recalled that animals in the postcataleptic state are much more susceptible to the effects of small doses of bulbocapnine than normal cats.

Changes in Muscle Tonus in Cataleptic Cats.—In the acute stages of catalepsy there are mild but evident changes in the tonus of the muscles of the limbs. These changes are similar to those occurring in cats with lesions in the red nuclei; there are noticeable positive proprioceptive *Stütz* reactions and resistance to passive flexion. These reactions are most readily obtained when the animal is suspended in a hammock with the limbs hanging free. A normal cat in this situation flexes the limbs and does not respond to pressure on the pads of the feet in the manner of the positive *Stütz* reaction, except by avoidance movements, but when there is increased tonus of the extensor muscles as a result of lesions the reactions are strongly positive. A further characteristic of the early stages of catalepsy is the readiness with which these reactions may be elicited when the cat is supine. In this regard such animals resemble decerebellate or rubrectomized cats.

In general it may be said that the changes in tonus are not ordinarily so uniformly evident, according to these tests, in cataleptic animals as in cats with lesions in the red nuclei. However, the animals with marked catalepsy show an extremely plastic type of rigidity, with good lengthening and shortening reactions which may persist after the *Stütz* reaction has disappeared, and a standing animal may be molded in various poses, as already described.

All the cats with prolonged catalepsy showed increased tonus of the extensor muscles, as indicated by the positive *Stütz* reaction, in the early stages. These changes varied in degree from day to day and gradually diminished so that the barest traces persisted at the end of a month. There was also resistance to passive extension of the limbs, and when in the supine position these animals were less inclined to hold the limbs extended than are rubrectomized cats. When the cats were suspended in the hammock the limbs were usually slightly flexed. However, the profoundly cataleptic cats gave an impression of great rigidity, and some animals, for instance, cats 9, 52 and 54, when picked up and supported by a hand placed beneath the belly showed a striking

extension and stiffness of the limbs, together with surprising rigidity of the muscles of the abdomen and trunk. In several of these cats the stiffness of the axial muscles was so great that the whole body could be elevated by a hand placed under the chin.

In cats with transient catalepsy the findings in regard to the *Stütz* reactions and resistance to passive flexion were the same. When the tonus reactions were most persistent there were usually abnormalities of gait, although this parallelism was not absolute, since in cats 20, 281 and 282 the gait showed marked disturbances of a "cerebellar" type but the changes in tonus were very slight. Several animals which showed practically no catalepsy but which had lesions somewhat similar to those of cataleptic cats showed tonus reactions resembling those found in the latter. The inference to be drawn is that increases of tonus of the extensor muscles, as shown by positive *Stütz* reactions and resistance to passive flexion, are incidental to, but not necessarily components of, the cataleptic syndrome in these animals.

Blood Calcium.—In searching for points of comparison between catatonic dementia praecox and the experimental catalepsy produced by bulbocapnine, Buscaino [4] pointed out an apparent diminution of serum calcium and potassium and hydration of the blood, which are present in both conditions. Gullotta [5] found rises of from 10 to 20 per cent in the blood calcium level in catatonic patients after administration of amytal, which interrupts the catatonic state. Administration of bulbocapnine to patients [6] is also said to cause hypocalcemia, supposedly as a result of an effect of the drug on hypothalamic centers. Katzenelbogen and Meehan [7] also observed a lowered blood calcium level after administration of bulbocapnine. It was therefore thought worth while to make a series of determinations of blood calcium on cataleptic cats in our series, and to compare the estimations made after operation with those made several days before operation. The Cramer and Tisdall modification of the method of Clark and Collip was used. The blood was drawn from the heart. The data on eleven animals are given in table 2. The serum calcium content is given in milligrams per hundred cubic centimeters of blood.

4. Buscaino, V. M.: Catatonia sperimentale nell'uomo, Riv. sper. di freniat. **58**:5, 1933.

5. Gullotta, S.: Sulla interruzione della sindrome catatonica, Riv. di pat. nerv. **40**:24, 1932.

6. Gullotta, S.: Le variazioni del calcio nella demencia precoce e sotto l'influenza della bulbocapnina, Boll. d. Soc. ital. di biol. sper. **5**:504, 1930.

7. Katzenelbogen, S., and Meehan, M. C.: The Chemistry of the Blood and the Cerebrospinal Fluid, with Special Reference to Calcium in the Cataleptoid State Induced by Bulbocapnine: The Combined Effect of Bulbocapnine and Some Other Drugs, J. Pharmacol. & Exper. Therap. **47**:131, 1933.

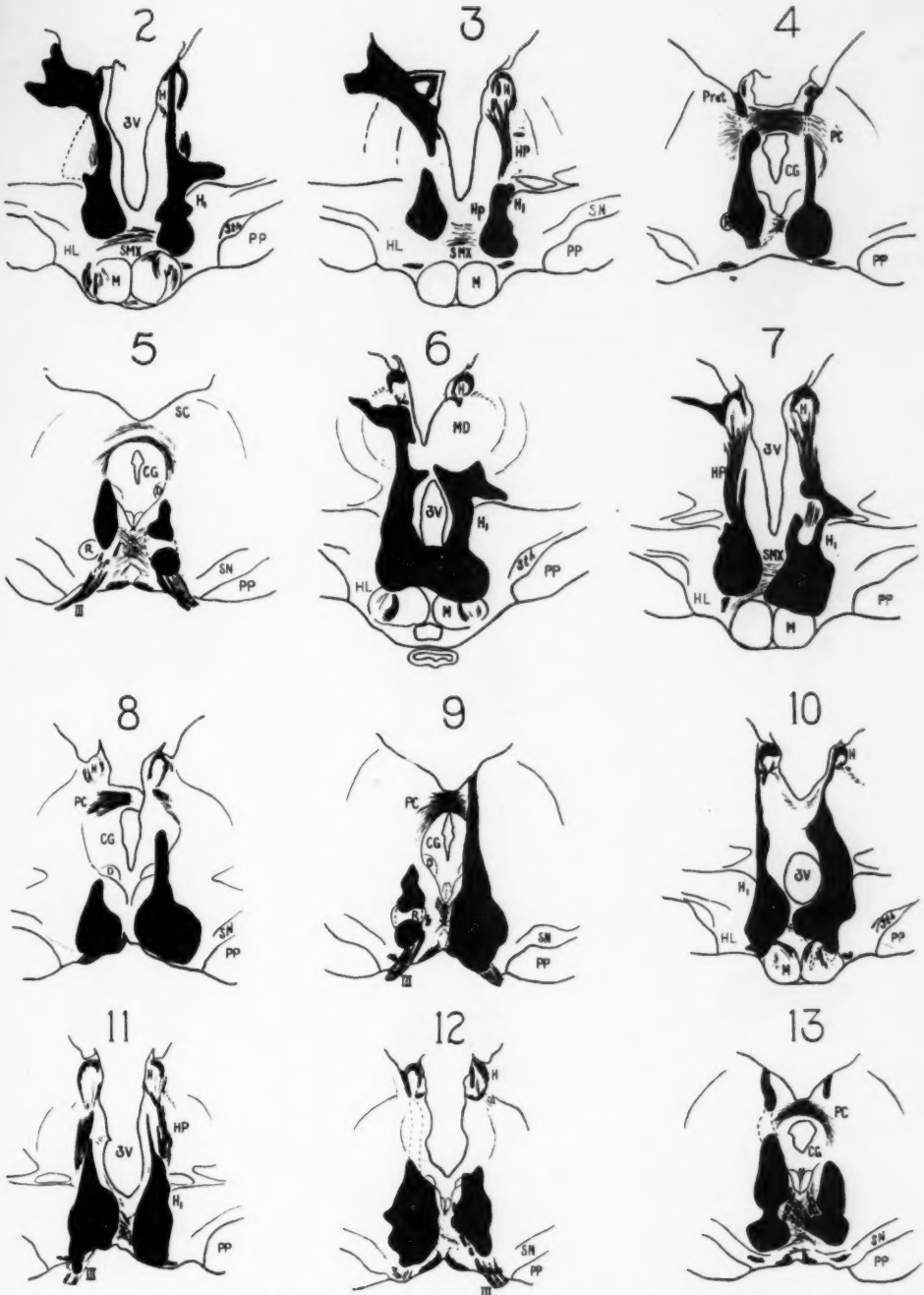
Although five of the eleven cats showed postoperative blood calcium levels which might appear to be significantly low, it is a question whether these levels are out of the normal range. We are not as yet ready to conclude from such figures that hypocalcemia is necessarily a constituent of the cataleptic syndrome in cats. Only two of six animals on which several preoperative determinations were made showed signs of any significant drop.

TABLE 2.—*Blood Calcium Content of Cataleptic Cats*

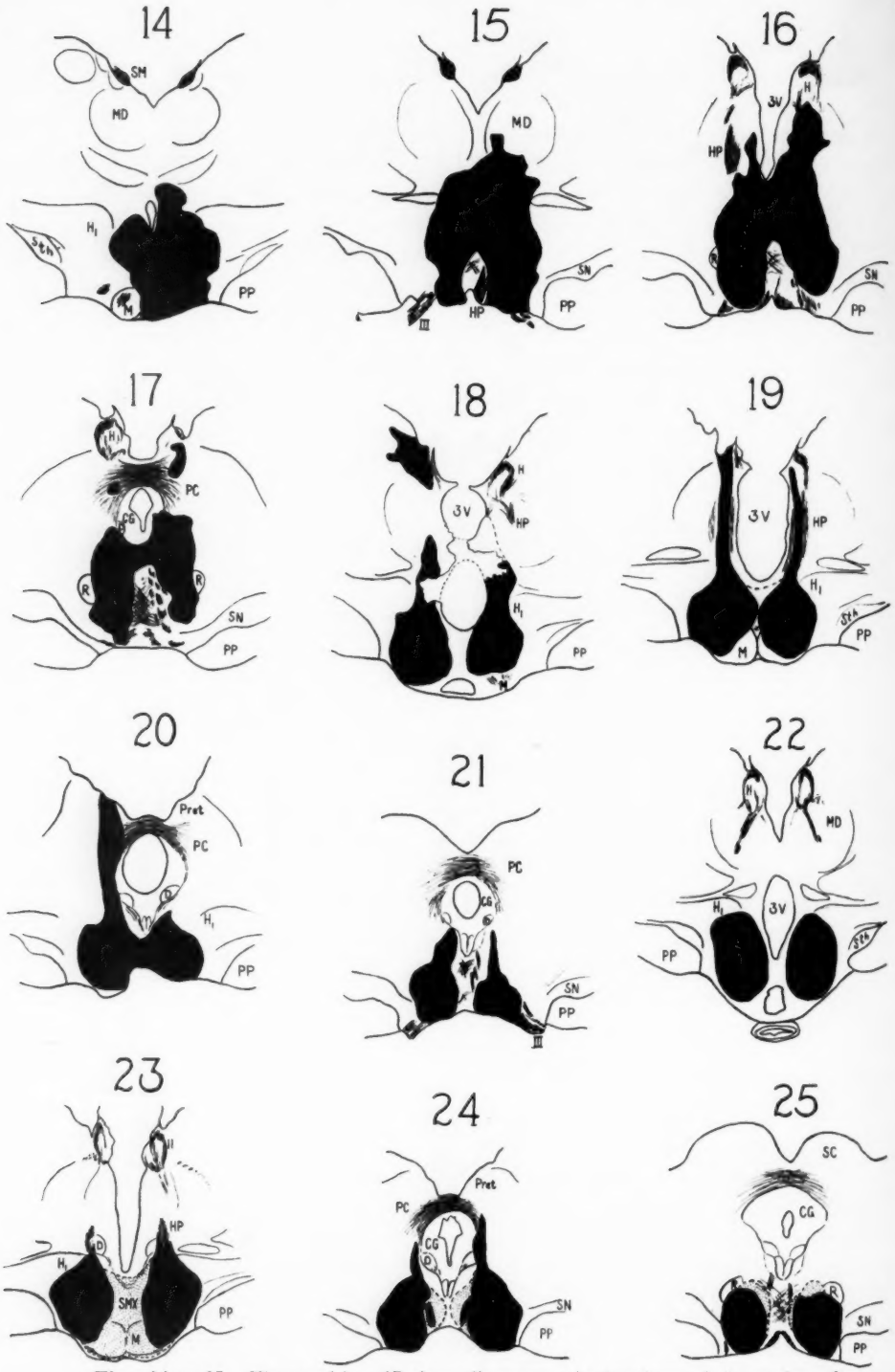
	Preoperative Period		Postoperative Period	
Cat	Time Before Operation	Blood Calcium, Mg. per 100 Cc.	Days After Operation	Blood Calcium, Mg. per 100 Cc.
138	1 hour	11.10	2	10.87
			6	9.92
			8	9.73
			10	9.82
140	1 hour	10.89	2	10.30
141	1 hour	10.99	4	10.26
142	1 hour	9.82	2	8.92
143	1 hour	11.20	1	10.17
			7	10.71
146	12 days	12.40	1	10.45
	11 days	11.44	6	11.13
	1 hour	11.59		
147	16 days	10.96	3	10.45
	15 days	11.77		
	14 days	10.96		
	9 days	11.81		
	1 hour	11.36		
148	16 days	10.66	3	11.36
	15 days	10.22	5	11.36
	14 days	11.70	8	11.13
	9 days	11.81		
149	17 days	11.99	2	10.90
	16 days	10.22	8	11.13
	15 days	11.55		
	10 days	10.90		
	1 hour	11.47		
154	4 days	11.36	2	10.90
	3 days	12.04	4	10.90
	2 days	11.59	7	10.68
155	5 days	11.36	1	10.45
	4 days	11.36	3	11.13
	3 days	10.45	6	10.90
Average		10.85		10.15

LESIONS

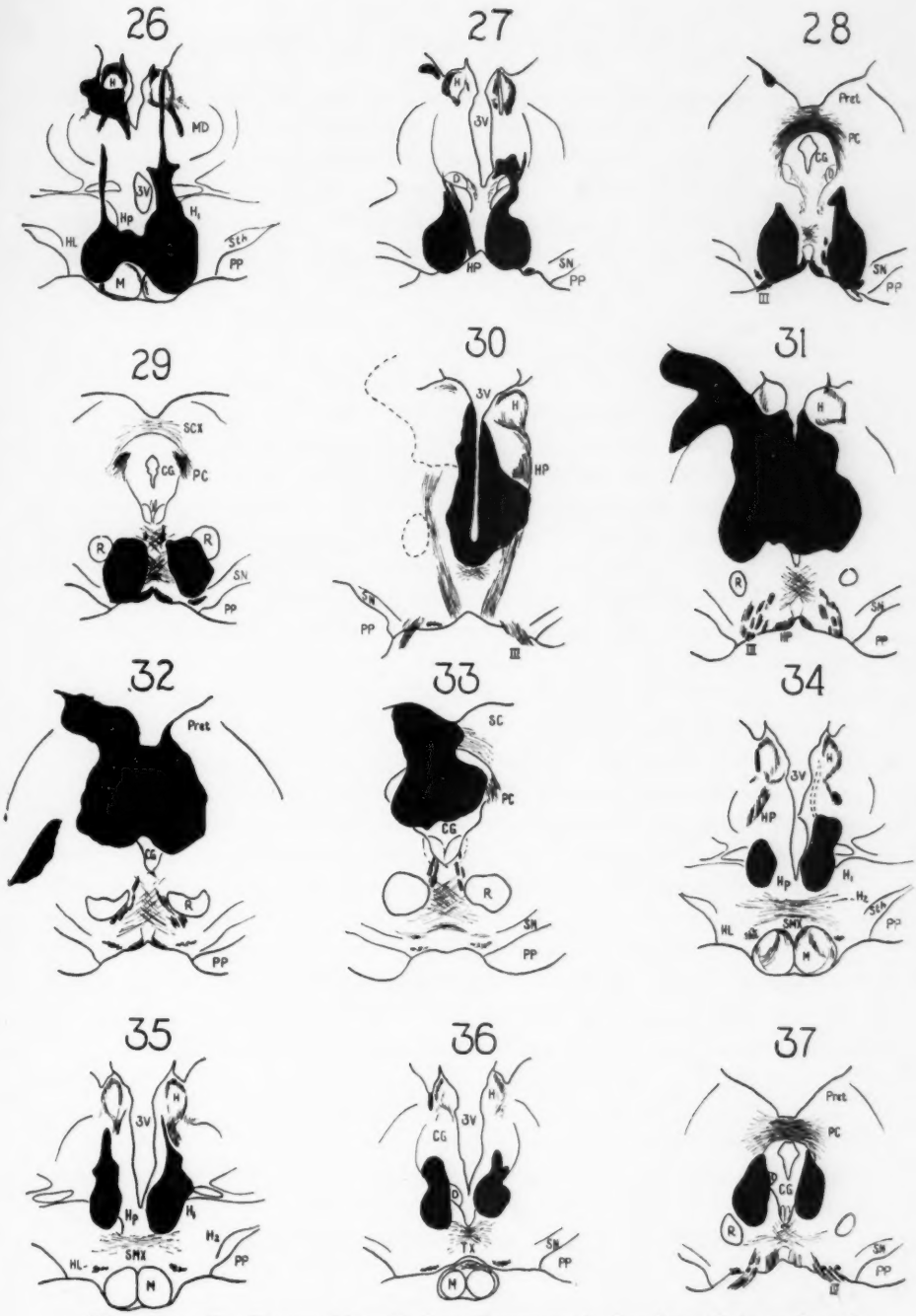
The lesions placed in the cats of which protocols have been given are illustrated in figures 2 to 29. These were all animals in which the symptoms were of long duration. It is assumed that such animals offer the best evidence as to the location of the structure or structures destruction of which leads to the syndrome described. Material from animals subjected to acute experiments or from animals with transient catalepsy is unreliable because the symptoms may have been due not to the visible lesions but rather to the temporary involvement of neighboring structures in the zone of reaction surrounding the lesion.



Figs. 2 to 13.—Figures 2 to 5 show diagrammatic drawings of the region of transition between the forebrain and the midbrain in cat 283. The lesions are indicated in black. Figures 6 to 9 show diagrammatic drawings of the region of transition between the forebrain and the midbrain in cat 291. The lesions are indicated in black. Figures 10 to 13 show diagrammatic drawings of the region of transition between the forebrain and the midbrain in cat 5. The lesions are indicated in black. In these and in the subsequent figures the following symbols are used: *CG*, central gray matter; *D*, nucleus of Darkshevich; *H*, habenula; *HL*, lateral hypothalamic area; H_1, H_1 field of Forel; H_2, H_2 field of Forel; *Hp*, posterior hypothalamic nucleus; *HP*, habenulopeduncular tract; *M*, mamillary body; *MD*, nucleus medialis dorsalis of thalamus; *PC*, posterior commissure; *PP*, pes pedunculi; *pret*, pretectal area; *R*, red nucleus; *SC*, superior colliculus; *SCX*, commissure of superior colliculus; *SM*, stria medullaris; *SMX*, supramamillary decussation; *SN*, substantia nigra; *Sth*, nucleus subthalamicus; *TX*, tegmental decussation; *3V*, third ventricle; *III*, third nerve.



Figs. 14 to 25.—Figures 14 to 17 show diagrammatic drawings of the region of transition between the forebrain and midbrain in cat 7. The lesions are indicated in black. Figures 18 to 21 show diagrammatic drawings of the region of transition between the forebrain and midbrain in cat 9. The lesions are indicated in black. Figures 22 to 25 show diagrammatic drawings of the region of transition between the forebrain and midbrain in cat 52. The lesions are indicated in black. Areas in which the myelinated fibers are degenerated are indicated by stippling.



Figs. 26 to 37.—Figures 26 to 29 show diagrammatic drawings of the region of transition between the forebrain and the midbrain in cat 54. The lesions are indicated in black. Figures 30 to 33 show diagrammatic drawings of the region of transition between the forebrain and the midbrain in cat 20. The lesions are indicated in black. Figures 34 to 37 show diagrammatic drawings of the region of transition between the forebrain and the midbrain in cat 282. The lesions are indicated in black.

The lesions, as shown in the drawings, extended from the level of the rostral pole of the mamillary bodies to the third nerve and were largest near the ventral surface of the brain stem, with extensions dorsally along the sides of the cerebral aqueduct and third ventricle. The most obvious features were involvement of the posterior hypothalamic nucleus, which borders the caudal part of the third ventricle, severe injury to the supramamillary area, including the region just dorsolateral to the mamillary bodies, and destruction of the region immediately caudal to the mamillary bodies. The involvement of the latter region usually includes the interruption of the habenulopeduncular tracts and of the rostral portion of the tegmental decussations. The destruction here is of relatively wide extent, but in no case have the cerebral peduncles or substantia nigra been affected. The rostral poles of the red nuclei may be destroyed, but the magnocellular portions usually remain intact. It does not seem to be essential that the lateral hypothalamic areas be entirely destroyed, although practically the entire extent of these areas was involved bilaterally in one of the most markedly cataleptic cats (cat 52; fig. 23). Injury to the dorsal thalamus, the posterior commissure and related structures, the gray matter of the caudal part of the third ventricle and aqueduct, the H_1 fields, the central tegmental fasciculi, etc., seems to be merely incidental, although injury to certain of these parts may cause motor disorders. Lesions in these regions but not involving the more basal areas do not produce catalepsy. The nonobstructive dilatation of the third ventricle which frequently occurred in these cataleptic animals was also found in some cats with more transient symptoms.

COMMENT

Special interest attaches to cats 20, 267, 274 and 282, in which the lesions were situated far dorsally and involved the central gray matter of the caudal part of the third ventricle and that surrounding the rostral part of the aqueduct. The lesions in two of these animals are indicated in figures 30 to 37. These animals were not cataleptic at any time. These negative results are of importance in view of the common belief that damage to the central gray matter in this region of transition between the third ventricle and the aqueduct is responsible for the cataleptic syndrome in cases of epidemic encephalitis.[8] The region damage to which produces catalepsy is fairly restricted. The syndrome is not produced by lesions farther forward in the hypothalamus in front

8. von Economo, C.: Die Pathologie des Schlafes, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 17, p. 591.

of the mamillary bodies [9] or by bilateral destruction of the red nuclei.[10]

The similarities between the feline catalepsy described here and that produced by bulbocapnine have been discussed in another paper.[2] The resemblance to certain types of catalepsy in man might also be pointed out, but a discussion of possible application of our experimental results to psychiatric studies on man is futile at the present time, although some neurologists apparently discern certain definite subcortical factors in cases of mental disease. The bearing of these experiments on the problems of muscle tonus, sleep and emotional expression, however, can hardly be denied.

The changes in tonus and motor disorders observed in the cataleptic cats are due to damage to extrapyramidal structures. In none of the animals in the series was a direct insult carried to the corticospinal system. The association of plastic rigidity and abnormality of gait with lesions of the hypothalamus and retromamillary tegmentum appears to be of some significance. Lesions of the neighboring red nuclei do not produce both of these phenomena. Lesions dorsolateral to the red nuclei, in the region of the central tegmental fasciculus, produce merely dysmetria of gait (cats 20 and 282). Loss of the structures rostral to the mamillary bodies produces mild hypertonia and does not make walking impossible.[11] One might assign reponsibility for the motor disorders we have described to the corpus striatum, but in our experiments no direct damage was done to this structure, and according to the work of Morgan [12] the pathways descending from the striate bodies in the cat do not pass through the areas involved by the lesions placed in our experiments. However, Lewy [13] has observed somewhat similar disturbances following bilateral lesions of the lentiform nuclei in monkeys. He describes poverty of movement, uncertainty, clumsiness and waxy rigidity of the muscles, which phenomena were accentuated to the point of complete helplessness when such lesions were combined with destruction of the central convolutions of the cortex. Regardless

9. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Relation of Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935.

10. Ingram, W. R., and Ranson, S. W.: Effects of Lesions in the Red Nuclei in Cats, Arch. Neurol. & Psychiat. **28**:483 (Sept.) 1932.

11. Hinsey, J. C.; Ranson, S. W., and McNattin, R. F.: The Rôle of the Hypothalamus and Mesencephalon in Locomotion, Arch. Neurol. & Psychiat. **23**:1 (Jan.) 1930.

12. Morgan, L. O.: The Corpus Striatum: A Study of Secondary Degenerations Following Lesions in Man and of Symptoms and Acute Degenerations Following Experimental Lesions in Cats, Arch.Neurol. & Psychiat. **18**:495 (Oct.) 1927.

13. Lewy, F. H.: Die Lehre vom Tonus und Bewegung, Berlin, Julius Springer, 1923.

of their association with the corpus striatum, however, such symptoms in cats as we have described are certainly associated with extensive injury to the reticular formation of the tegmentum just rostral to the red nuclei. The importance of the tegmental reticular formation in general for the carrying out of postural, righting and tonus reactions has been suggested by us before.[14] It seems no less apropos to suggest that some structure affected by the lesions in these cats is important for maintaining a labile balance of muscle tonus and general readiness for activity.

While somnolence has been repeatedly produced by experimental methods and catalepsy has been found to result from the administration of such drugs as bulbocapnine, the picture of pathologic sleep and plasticity as resulting from experimental lesions in animals has been described in few instances. The work of Lewy has already been cited. Demole,[15] in reporting the results of experiments with the injection of small quantities of calcium and potassium salts into the neighborhood of the third ventricle, described a cat in which the injection was presumably made in the para-infundibular gray matter between the tuber cinereum and the mamillary bodies. This animal showed stupor, muscle tonus above normal, slight stiffness and "passivity similar to catatonia." It remained in induced positions, as with limbs spread, lying on its back with its head raised or lowered. The lateral position was slowly resumed. Demole [16] ventured to prophesy the eventual approach to the study of catatonia by experimental methods. A sort of catalepsy has also been observed by Seletzky and Gilula [17] to follow section of the corpus callosum; whether this is in any way identifiable with the catalepsy seen in our experiments cannot be determined.

We have been concerned in this paper primarily with catalepsy as it expresses itself in the skeletal muscles. Since it is often difficult to determine whether a cat is awake or asleep and since such observations are much more easily made on monkeys, a discussion of the somnolence which can be produced by lesions at the base of the brain in the region of transition between the forebrain and the midbrain will be reserved until the experiments now being conducted on monkeys are complete. It may be said, however, that somnolence can be produced in these animals by damage to the hypothalamus. A brief reference to these

14. Ingram, W. R.; Ranson, S. W., and Barris, R. W.: The Red Nucleus: Its Relation to Postural Tonus and Righting Reactions, Arch. Neurol. & Psychiat. **31**:768 (April) 1934.

15. Demole, V.: Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:228, 1927.

16. Demole, V.: Catatonie expérimentale, Rev. neurol. **1**:861, 1927.

17. Seletzky, W., and Gilula, J.: Zur Frage der Funktionen des Balkens bei Tieren, Arch. f. Psychiat. **86**:57, 1928.

experiments and their significance for an understanding of the nature and cause of sleep has already been published.[18]

SUMMARY

Catalepsy has been produced in cats by lesions at the base of the brain in the region of transition between the midbrain and the forebrain. The evidence indicates that the symptoms are caused by damage to some structure or structures in the neighborhood of the mamillary bodies, such as the posterior hypothalamic nucleus, the supramamillary area, the lateral hypothalamic area and the region just caudal to the mamillary bodies. A more specific localization cannot be given at this time.

In the days immediately following the operation the cats were somnolent and showed marked plastic tonus of the muscles. In the later stages there remained an increased plasticity of the muscles, expressed in the maintenance of odd postures, and often abnormalities of behavior, such as pronounced lack of motor initiative, stolidity and subnormal emotional expression, were observed. There was a disinclination to eat, and the cats required artificial feeding.

Tracings of the respiratory movements showed that the animals responded by changes in the rhythm or extent of respiratory movement to stimuli which produced no directly observable motor response.

There was no clearcut evidence of change in the calcium content of the blood.

The syndrome did not develop in cats in which there was extensive damage to the central gray matter of the aqueduct and third ventricle but in which the mamillary bodies and surrounding parts escaped injury.

18. Ranson, S. W.: The Hypothalamus: Its Significance for Visceral Innervation and Emotional Expression, Tr. Coll. Physicians Philadelphia **2**:222, 1934.

OXYGEN SATURATION OF THE ARTERIAL BLOOD IN EPILEPSY

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Because nerve tissue, more than any other tissue of the body, is dependent on oxygen for its proper functioning and because it has been shown [1] that seizures may be precipitated in patients who have frequent attacks of petit mal by the breathing of air deficient in oxygen, the question of whether blood going to the brain of persons with epilepsy has a normal oxygen tension is a pertinent one. So far as we are aware, no attempt has been made to shed light on this question.

MATERIALS AND METHODS

The patients examined were under treatment for epilepsy and were private or hospital patients. No division of the patients on the basis of etiology was attempted. The hearts and lungs of all were found to be normal by routine methods of examination. In every instance blood was taken with the patient recumbent after a ten minute or longer period of rest. Blood was drawn from a femoral, radial or brachial artery after the overlying skin and the surrounding tissues had been infiltrated with procaine hydrochloride. The blood was taken under oil, immediately chilled and analyzed in the apparatus and by the method described by Van Slyke.[2] The percentage of oxygen saturation of the blood was determined by dividing the oxygen content of the blood by its oxygen capacity. The content is the volume of oxygen contained in the blood when it is drawn; the capacity is the volume contained after the blood has been fully exposed to air by rotation in a cylindric funnel. In some laboratories the blood is exposed to air which contains an amount of carbon dioxide corresponding to that of the alveolar air. This method reduces slightly the oxygen capacity and thereby increases the oxygen saturation. The values for the blood of normal persons as found in the literature were, however, obtained by the method of collection of the blood and of exposure to atmospheric air, which we have used.

From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital. This paper is no. XIX in a series entitled "Studies in Epilepsy." Assistance in this research was received from the Harvard Epilepsy Commission.

1. Lennox, W. G.: The Effect on Epileptic Seizures of Varying the Composition of Respired Air, J. Clin. Investigation **6**:23, 1928. Lennox, W. G., and Cobb, S.: Epilepsy from the Standpoint of Physiology and Treatment, Baltimore, Williams & Wilkins Company, 1928.

2. Van Slyke, D. D.: Portable Form of the Manometric Gas Apparatus and Certain Points in the Technique of Its Use, J. Biol. Chem. **73**:121, 1927.

OBSERVATIONS

One hundred and twenty-five measurements were made on eighty-eight patients. In the eighty-eight cases the oxygen saturation of the blood drawn at the initial puncture averaged 93.4 per cent. The average value on subsequent punctures was only 91.9 per cent, because patients who showed initial low values were more often selected for repeated punctures. The saturation in normal persons is between 94 and 99 per cent. Therefore, the average oxygen saturation of the arterial blood of our patients with epilepsy was below the limits of normal.

The distribution of measurements is displayed in the middle column of table 1. Of the eighty-eight initial measurements, 54 per cent were in the normal zone of 94 per cent saturation or above; 46 per cent were below the lower limit, and 11 per cent were below 90 per cent saturation.

TABLE 1.—*Oxygen Saturation of Arterial Blood*

	Percentage Distribution of Various Saturations		
Percentage of Oxygen Saturation	Healthy Persons (Literature) Percentage	88 Patients with Epilepsy, Percentage	58 Ward Patients with Neurologic Diseases, Percentage
99 to 94	100	54	46
93.9 to 90	...	35	45
89.9 to 85	...	11	9
Total	100	100	100

The hypoxemia requires explanation. In order to ascertain whether arterial hypoxemia is a condition peculiar to persons with epilepsy, the blood gases of fifty-eight patients with nonepileptic neurologic diseases were measured. These patients were mostly confined to bed with such conditions as multiple sclerosis, progressive muscular atrophy, neuritis and neurosis. None had significant pulmonary or cardiac lesions. This group of fifty-eight patients had an average oxygen saturation of the arterial blood of 93.1 per cent, which is a trifle lower than the value for persons with epilepsy. The distribution of readings differed somewhat in that in the group of patients without epilepsy there were fewer values in the normal zone (last column of table 1). Only 46 per cent of the patients without epilepsy had a saturation of 94 per cent or greater. In 45 per cent the saturation was below the lower limit of normal, and in 9 per cent it was less than 90 per cent. Therefore, the condition of decreased oxygen saturation of the arterial blood is not peculiar to persons with epilepsy but is present in an even larger proportion of patients with nonepileptic neurologic disease. The average carbon dioxide content of the arterial blood of persons with epilepsy

was 48.6 volumes per cent, and that of the arterial blood of patients with neurologic disease was 48.5 volumes per cent, which are normal values.

Defective aeration of the arterial blood (in the absence of deficiency of oxygen in the respired air) may be due to: (1) excessive speed of the flow of blood through the pulmonary capillaries, (2) reduced permeability to oxygen of the alveolar or capillary walls and (3) deficient alveolar ventilation.

As regards the first point, it has been shown that the administration of atropine, which increases the speed of the flow of blood through the lungs, decreases the oxygen saturation of the arterial blood, but persons with epilepsy, we have found, have a normal circulation time. Binger, Brow and Branch [3] observed that the oxygen content of arterial blood could be reduced 20 to 30 per cent if the majority of the capillaries of the lung were blocked. The blood traversed the unblocked vessels too fast to permit proper exchange of blood gases. As regards this (and the second point), patients presented no evidence of pathologic conditions of the lungs. As for the third point, it has been shown that mild hypoxemia results from defective pulmonary ventilation. Hurtado and his associates [4] found that the average oxygen saturation of the arterial blood of twenty-four patients with emphysema was 88 per cent and that of thirty-seven patients with pulmonary fibrosis was 92 per cent. They stated that when the residual air of the lungs constitutes 45 per cent or more of the total lung capacity, some arterial anoxemia always results. It is known also that a period of voluntary shallow breathing will cause a measurable decrease in the oxygen content of the arterial blood.

In order to test this point of defective pulmonary ventilation in our cases, and as a check on the reliability of our technic of measurement of blood gases we conducted a series of experiments to determine whether increasing the tension of oxygen in the alveoli would correct the existing hypoxemia.

Certain patients, both persons with and persons without epilepsy, who had an abnormally low oxygen saturation of the arterial blood were asked to overventilate their lungs voluntarily for a minute or two or to respire pure oxygen from a spirometer. Twenty experiments were

3. Binger, C. A. L.: Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing: II. Tachypnea, Dependent upon Anoxemia, Resulting from Multiple Emboli in the Larger Branches of the Pulmonary Artery, J. Clin. Investigation **1**:155, 1924.

4. Hurtado, A.; Kaltreider, N. L., and McCann, W. S.: Studies of the Total Pulmonary Capacity and Its Subdivisions: IX. Relationship to the Oxygen Saturation and the Carbon Dioxide Content of the Arterial Blood, J. Clin. Investigation **14**:94 (Jan.) 1935.

carried out. In every instance except one, blood taken during the period of overventilation or of breathing oxygen had both an increased and a normal oxygen saturation. The average measurements are given in table 2. As a result of overventilation the oxygen saturation of the arterial blood increased from 93.2 per cent before breathing to 96.3 per cent during the breathing. As a result of the breathing of oxygen it increased from 92.5 to 98.9 per cent. Therefore, the mild anoxemia present in a majority of the patients with epilepsy and other conditions who were examined is explained by their defective pulmonary ventilation.

A partial explanation of the defective pulmonary ventilation may be the circumstance that blood was drawn with the patients in the lying position, whereas many of the healthy subjects of experiments reported in the literature were sitting. Calhoun and his associates [5] found the average saturation of the arterial blood in a group of eight patients

TABLE 2.—*Effect of Voluntary Pulmonary Ventilation and of Breathing of Oxygen on Oxygen Saturation of the Arterial Blood*

Procedure	Number of Cases	Oxygen Content, Percentage by Volume	Oxygen Capacity, Percentage by Volume	Oxygen Saturation, Percentage
Before overventilation	6	17.1	18.4	93.2
During overventilation	6	17.7	18.4	96.3
Before breathing of oxygen	14	17.1	18.5	92.5
During breathing of oxygen	14	18.4	18.6	98.9

with cardiac disease to be 88.3 per cent when the subject was lying down and 91.5 per cent when the subject was sitting. We believe, however, that the principal difficulty with patients with epilepsy and other neurologic diseases is the fact that the majority had a poor posture, a poor chest expansion and a poor general physique.

COMMENT

The degree of hypoxemia which the majority of patients exhibited is not in itself sufficient to explain the seizures to which these patients are subject. The lowest oxygen saturation of the arterial blood, around 86 per cent, is comparable with the oxygen saturation of the arterial blood of acclimated persons at an elevation of about 14,000 feet (4,267 meters). It is possible, however, that even this mild degree of oxygen lack in the blood reaching the brain might be a contributory factor in

5. Calhoun, A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. L., and Tims, M. M.: Studies in Congestive Heart Failure: XIV. Orthopnea; Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, J. Clin. Investigation **10**:833, 1931.

seizures. At any rate, it indicates that the patients in question are not in the best physical condition. Observations showing the influence on seizures of artificially altering the oxygen tension of respired air have been set forth elsewhere,[6] as has the question of the state of the venous blood.[7]

CONCLUSIONS

The oxygen saturation and carbon dioxide content of the arterial blood were measured one hundred and twenty-five times in eighty-eight patients with epilepsy. In 46 per cent of the patients the initial measurement of the oxygen saturation was below the lower normal limit of 94 per cent, and in 11 per cent it was below 90 per cent. The average measurement was 93.4 per cent.

This degree of anoxemia is not peculiar to patients with epilepsy; it is present also in patients with other neurologic diseases. It could be abolished by deep breathing or by the inhalation of oxygen and is believed to be an expression of the defective pulmonary ventilation in these patients. It is insufficient in degree to be considered a cause of seizures, except perhaps a contributing cause.

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6. Lennox, W. G., and Behnke, A. R., Jr.: Effect of Increased Oxygen Pressure on the Seizures of Epilepsy, Arch. Neurol. & Psychiat. **35**:782 (April) 1936.

7. Lennox, W. G., and Gibbs, E. L.: Blood Draining the Brain and the Limbs of Epileptics with Reference to Its Oxygen Saturation, Arch. Neurol. & Psychiat., to be published.

EFFECT OF CERVICOTHORACIC SYMPATHECTOMY ON HEADACHES

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Since headache is such a frequent complaint and since operations on the cervical and cervicothoracic portions of the sympathetic nervous system have been performed for its relief, we believed it worth while to review cases observed at the Mayo Clinic in which operations on these portions of the sympathetic nervous system had been performed for conditions other than headache in order to determine the effects of such operations on patients who complained of headaches in addition to the primary disease.

TREATMENT OF HEADACHE

The treatment of headache and of one of its classic types, migraine, has been an enigma since earliest times. The approach to the problem has been both medical and surgical. Prehistoric skulls have been uncovered in which a trephine opening had been placed, apparently in an attempt to let out the evil spirit and allay the suffering of severe headache. Treatment today runs the gamut of sedative and analgesic drugs, vasodilators, sympathetic depressants, diets, avoidance of certain foods and many different types of surgical procedures. This bears testimony to the protean nature of headache and the lack of satisfactory results in all cases from any one type of treatment.

Medical Treatment.—Medical treatment [1] consists in the avoidance of excessive stress and strain and emotional upsets, the regulation of habits of living and eating, the taking of sedative or analgesic drugs at the onset or during the attack of headache and rest in bed with the application of cold compresses or an ice cap to the head.

In May 1934, Lennox [2] reported the use of ergotamine tartrate (gynergen) in the treatment of migraine. The results obtained by him

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From the Section on Neurologic Surgery, the Mayo Clinic.

1. (*a*) Alvarez, W. C.: The Present Day Treatment of Migraine, Proc. Staff Meet., Mayo Clin. **9**:22 (Jan. 10) 1934. (*b*) Logan, A. H., and Allen, E. V.: The Treatment of Migraine with Ergotamine Tartrate, ibid. **9**:585 (Sept. 26) 1934.

2. Lennox, W. G.: The Use of Ergotamine Tartrate in Migraine, New England J. Med. **210**:1061 (May 17) 1934.

and by others [1b] offer hope for the more successful relief of migraine by medical measures in the future.

Surgical Treatment.—The operative treatment of severe headache and migraine is not standardized. The various surgical procedures which have been advised and carried out by different surgeons indicate that no type of operation will relieve symptoms in all cases, and there is no reliable way of determining what patients will obtain relief and which operation is indicated for the particular subject under consideration.

Jonnesco,[3] before 1923, performed bilateral cervical sympathectomy for migraine in one case, with good results. In 1930 Mixter and White [4] reported success in several cases in which they had performed cervicothoracic sympathectomy for the relief of paresthetic symptoms following division of the sensory root of the fifth cranial nerve for trigeminal neuralgia. Before this, in 1928, Frazier [5] had failed to relieve atypical neuralgia by operations on the cervical portion of the sympathetic nervous system. Dandy,[6] in 1931, reported two cases of migraine in which he was able to relieve the condition by cervicothoracic sympathetic ganglionectomy. In one of these cases he had been unable to bring about relief previously by removal of the superior cervical ganglion. Craig [7] performed cervicothoracic sympathectomy for migraine in two cases, and complete relief resulted. Before carrying out this operative procedure it is at times advisable to block the cervicothoracic ganglia with procaine hydrochloride during an attack to determine what influence the sympathetic system has in the production of the pain. If anesthetization of the sympathetic ganglia stops the migraine, operation should result in permanent relief.

In addition to operations on the sympathetic nervous system, ligation and division of the middle meningeal artery have brought about relief from severe headache.[8] In Craig's case the patient complained of a

3. Jonnesco, T., cited by Riley, H. A.: Migraine, Bull. Neurol. Inst. New York **2**:429 (Nov.) 1932.

4. Mixter, W. J., and White, J. C.: Pain Pathways in the Sympathetic Nervous System: Clinical Evidence, Tr. Am. Neurol. A., 1930, p. 433; Arch. Neurol. & Psychiat. **25**:986 (May) 1931.

5. Frazier, C. H.: Atypical Neuralgia: Unsuccessful Attempts to Relieve Patients by Operations on the Cervical Sympathetic System, Arch. Neurol. & Psychiat. **19**:650 (April) 1928.

6. Dandy, W. E.: Treatment of Hemicrania (Migraine) by Removal of the Inferior Cervical and First Thoracic Sympathetic Ganglion, Bull. Johns Hopkins Hosp. **48**:357, 1931.

7. Craig, W. McK.: Hemicrania of Migraine, Proc. Staff Meet., Mayo Clin. **10**:362 (June 5) 1935.

8. Craig, W. McK.: Localized Headache Associated with Lesion of Meningeal Vessels, J. A. M. A. **100**:816 (March 18) 1933.

throbbing or pulsating type of headache, and at the time of operation the artery was found to be encased in a bony canal.

Others, notably Dickerson,[9] by ligating the middle meningeal artery have been successful in relieving headaches. One wonders whether in some of the cases ligation of the artery per se is the factor that brings about relief. Might not the relief result from interruption of sympathetic fibers accompanying the artery or from section of the recurrent branch of the mandibular nerve, which enters the skull through the foramen spinosum with the middle meningeal artery? Then, too, the mere presence of an opening made for decompression, although small, may have a beneficial effect.

It is interesting in reviewing cases of trigeminal neuralgia with migraine to note that the migraine is often relieved with the neuralgia after division of the sensory root of the fifth nerve. In this operation there are, of course, all three factors, namely, ligation of the middle meningeal artery, division of the recurrent branch of the mandibular nerve—in fact division of all sensory branches from the fifth cranial nerve to the dura on that side—and decompression.

The most recent operation for migraine is that devised by Adson [10] and reported before the staff of the Mayo Clinic on Nov. 7, 1934. Adson's operation consists in performing a periarterial sympathectomy of the common carotid artery, ligation and division of the external carotid artery and removal of the superior cervical sympathetic ganglion and the upper portion of the sympathetic trunk on the side on which the migraine occurs. Adson's patient was completely relieved of all discomfort in the head for six weeks after operation; however, this patient returned later and stated that he had had recurrence of headache. He also stated that he had resumed the use of a mixture of the hydrochlorides of the opium alkaloids and of amytal.

ANALYSIS OF CASES STUDIED

The cases of one hundred and twenty-six patients who between 1924 and Nov. 14, 1933, underwent operations on the cervicothoracic portion of the sympathetic trunk for the relief of Raynaud's disease, Raynaud's disease with scleroderma, thrombo-angiitis obliterans (Buerger's disease), chronic infectious arthritis and a small group of miscellaneous conditions were reviewed. As has been stated, eighteen of the patients complained of headaches of such severity and frequency that they constituted a major secondary complaint.

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9. Dickerson, D. G., cited by Bassoe, Peter: Migraine, J. A. M. A. **101**:599 (Aug. 19) 1933.

10. Adson, A. W.: Right Frontotemporal Migraine Relieved by Surgical Methods: Report of a Case, Proc. Staff Meet., Mayo Clin. **9**:673 (Nov. 7) 1934.

This study was concerned with the effect of operation on the headache of these eighteen patients, in seventeen of whom a bilateral cervicothoracic sympathectomy was performed and in one of whom the operation was on the right side alone.

Sixteen of the eighteen patients were followed, and replies were received from them during the course of this study. Twelve of the sixteen (75 per cent) were either partially or completely relieved, and four (25 per cent) stated that their headache had remained unchanged since operation. None complained of more severe headache after operation. Three patients were completely relieved of their headaches; all three of these had been operated on primarily for Raynaud's disease; in each case the headaches had been definitely migrainous. This result lends support to the vasospastic theory of migraine, for when the head and brain were completely deprived of all sympathetic innervation in the process of denervating the upper extremities for Raynaud's disease, the subjects ceased to suffer from periodic attacks of headache. It is of further interest to note that eight of the twelve patients (66 per cent) who obtained relief after cervicothoracic sympathectomy were in the group of those with Raynaud's disease. Of the other four who were partially relieved, one was operated on primarily because of arthritis, although there was, in addition, a mild form of Raynaud's disease and the headaches were migrainous, a patient who was operated on for hyperhidrosis was partially relieved; a patient with thrombo-angiitis obliterans was partially relieved of headache following bilateral cervicothoracic sympathectomy, and the fourth patient who obtained partial relief after operation had had atypical migrainous attacks for ten years. The operation in the last case, a cervicothoracic sympathectomy on the right side, was performed because of evidence of involvement of this part of the sympathetic nervous system. When the stellate ganglion was explored it was found to be the site of a new growth, a ganglioneuroma. The cervicothoracic ganglia, trunk and communicating rami were removed.

The cases of the four patients who were traced and who experienced no amelioration of headaches after the operation warrant consideration. One of these patients, who primarily had Raynaud's disease, also complained of a recurring migrainous type of headache that was usually associated with hysterical attacks. Another patient, operated on primarily because of arthritis, had complained of headaches for many years. These headaches had been definitely related to fatigue, and the patient presented many other symptoms that are included in the syndrome of chronic nervous exhaustion. The third patient had progressive organic disease of the central nervous system. Operation was performed in this case because of chronic encephalitis with severe oculogyric crises. The fourth patient whose headaches were not influenced by operation

also had Raynaud's disease, symptoms of which had been present for two years. There was a history of this patient's having had rather frequent headaches for a little over two years (table).

*Effect of Cervicothoracic Sympathectomy on Headaches Complained of by Eighteen of One Hundred and Twenty-Six Patients Who Were Operated on for Various Vasospastic Disturbances**

Primary Diagnosis	Total Number of Patients	Patients with Headache		Migraine			Unclassifiable Headache		
		Number	Percentage	Complete Relief	Partial Relief	Unchanged	Complete Relief	Partial Relief	Unchanged
Raynaud's disease with or without scleroderma	67	11	16.42	3	1	0	0	4	2
Thrombo-anglitis obliterans	22	1	4.54	0	0	0	0	1	0
Chronic infectious arthritis	16	3	18.75	0	1	0	0	0	1
Miscellaneous hyperhidrosis, encephalitis, etc.	21	3	14.29	0	0	0	0	2	1

* A patient with Raynaud's disease and one with chronic infectious arthritis could not be traced.

SUMMARY AND CONCLUSIONS

Seventy-five per cent of eighteen patients who complained secondarily of headache were either partially or completely relieved of the headaches when bilateral cervicothoracic sympathectomy (according to Adson's technic) was performed for some other condition. Sympathectomy was most effectual in relieving headache when it occurred in association with Raynaud's disease.

The relief of headache coincident with relief of a known vasomotor disturbance (Raynaud's disease) lends support to the view that severe headache occasionally, and migraine frequently, is the expression of a vascular crisis related in some way to a disturbance of the sympathetic nervous system.

It is apparent as a result of this study that cervicothoracic sympathectomy is effective in relieving a certain number of patients of periodic attacks of migraine. When a patient with migraine presents other symptoms indicating disturbance of the sympathetic nervous system, such as Raynaud's disease, cervicothoracic sympathectomy gives relief in about 75 per cent of cases. Cervicothoracic sympathectomy is justified in carefully selected cases of severe migraine.

POSTURAL REFLEXES IN PATIENTS WITH LESIONS OF THE FRONTAL LOBE

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Although the phenomenon of forced grasping was described before the classic report of Wilson and Walshe [1] in 1914, these authors were the first to associate it with lesions of the frontal lobe. This clinico-pathologic deduction received its first experimental confirmation in 1932. Richter and Hines [2] were able to produce a "grasp reflex" in adult monkeys by ablation of cortical area 6 of Brodmann, hereinafter referred to as the premotor zone or area. They stated:

> In summarizing them the lesion which results in the hanging response on the part of the heterolateral hand is the removal of area 6 anterior to the leg region of the motor cortex through to and including the medial surface. The removal of the comparable area in the opposite hemisphere brings out the reflex in the heterolateral hand as well as the homolateral.

Fulton and his co-workers [3] further investigated and elucidated this problem. In the course of their experiments with monkeys, preparations were employed in which the motor and premotor areas had been extirpated bilaterally. Such animals were unable to right themselves and presented in a lateral position a fundamental postural pattern originally described by Magnus [4] in thalamic animals.

> If such an animal is placed in the lateral position on a table, the underlying lower limb becomes extended, the upperlying one is flexed, and the pelvis simultaneously rotates toward the normal postural attitude. The reaction is independent of the position of the head in space. The receptors for the reflex are located on

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From the Neurological Division of the Montefiore Hospital.

Read at the International Congress of Neurologists, London, Aug. 2, 1935.

1. Wilson, S. A. Kinnier, and Walshe, F. M. R.: The Phenomenon of "Tonic Innervation" and Its Relation to Motor Apraxia, Brain **37**:199, 1914.

2. Richter, Curt P., and Hines, Marion: The Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions, A. Research Nerv. & Ment. Dis., Proc. **13**:211, 1932.

3. Fulton, J. F., and Kennard, Margaret A.: A Study of Flaccid and Spastic Paralyses Produced by Lesions of the Cerebral Cortex in Primates, A. Research Nerv. & Ment. Dis., Proc. **13**:158, 1932.

4. Magnus, R.: Koerperstellung, Berlin, Julius Springer, 1924, p. 243.

the lateral aspect of the trunk and lower extremities, and, to be sure, a widespread asymmetrical stimulation of the receptors is necessary. Simple pressure on the lower extremity or on the body flank is insufficient.

Although Magnus stressed only the postural changes in the lower extremity, it is apparent from his photographs that the upper limbs are similarly involved in the pattern.

In bilateral area 4 and 6 preparations it was observed [5] that forced grasping was present only in the uppermost or flexed extremities (in the left limbs with the animal in the right lateral position) and was not present in the underlying extended extremities. When the animal was placed in the left lateral position the same relationship was maintained; that is, grasping was present in the flexed right limbs. Anesthesia of the hand produced by subcutaneous infiltration with procaine hydrochloride did not abolish the grasp reflex or alter its relation to the postural pattern. From these observations Bieber and Fulton [5] concluded that "forced grasping and groping are the counterparts in primates of the more simple rhythmic movements to be seen in thalamic cats and dogs when attempting to right themselves; and that grasping as such is to be regarded as a part of the righting reflex mechanism peculiar to primates." Fulton also observed that even in unilateral area 6 preparations the grasp reflex is most easily elicited when the animal is in the lateral position with the affected limb uppermost: This position has come to be considered the "maximal" one for obtaining the reflex.

The clinical history of the phenomenon has been frequently reviewed. For a decade following the contribution of Wilson and Walshe the whole question lay dormant; then the phenomenon aroused renewed interest and has become the subject of numerous clinical investigations. From a physiologic point of view these may be summarized by the following quotation: [3] "Adie and Critchley, Richter and Hines, Brain and Curran, Schuster and Casper, and others who have studied the relation of the premotor area to forced grasping have concluded that it exerts an inhibitory influence on postural reflexes—particularly on the grasp reflex." In 1933 the report of Walshe and Robertson [6] did much to dispel the confusion in which the phenomenon had become involved. These authors resolved the grasping reflex into two components, one volitional and the other reflex. The volitional component, consisting of the grasping of the fingers with the occasionally associated movements of the hand and arm, was brought about by visual and tactile

5. Bieber, I., and Fulton, J. F.: The Relation of Forced Grasping and Groping to the Righting Reflexes, in preparation; preliminary communication in Am. J. Physiol. **105**:7, 1933.

6. Walshe, F. M. R., and Robertson, E. Graeme: Observations upon the Form and Nature of the "Grasping" Movements and "Tonic Innervation" Seen in Certain Cases of Lesions of the Frontal Lobe, Brain **56**:40, 1933.

stimuli. The nature of the responses to these stimuli was such that the authors declined to regard them as true reflexes "of the decorticate nervous system." The reflex component consisted of the tonic innervation of muscles when, and only when, these were subjected to the proprioceptive stimulus of stretch. Kennard, Viets and Fulton [7] demonstrated that in a patient with a lesion of the right premotor area the forced grasping varied in its intensity with the position of the patient. "However, when the patient turned his whole body to the right so that he was lying on his side, the reflex was increased very markedly in strength, so that the fingers were pulled away from the palm with considerable difficulty. When the patient turned on his left side, the reflex was somewhat diminished, but was practically the same as when he was lying on his back."

We have applied these physiologic and clinical observations to a group of four patients demonstrating forced grasping and to one patient with jacksonian epilepsy associated with pathologic changes in the premotor area in a further attempt to analyze the influences of posture on these phenomena. In the cases of forced grasping we were concerned only with the physiology of this reflex. Correlation with the localization of pathologic changes will not be attempted, as we are of the opinion that the relationship of this reflex to lesions of the premotor area has been adequately established.

REPORT OF CASES

CASE 1.—R. W., a woman aged 34, was admitted to the Montefiore Hospital with the history of sudden onset on April 4, 1934, of headache, stiff neck, pain down the back and vomiting. These symptoms began gradually to recede and disappear within two weeks. On April 22 there was a sudden recurrence of the symptoms, this time with loss of consciousness. The patient was admitted to the Neurological Institute on April 24, and examination revealed a Kernig sign bilaterally and nuchal rigidity. The spinal fluid was bloody, and the eyegrounds showed multiple striate hemorrhages. Two days later there rapidly developed total aphasia and right hemiplegia. On April 30 the temperature rose to 104 F.; the pulse rate and respiratory rate were elevated. An exploratory trephination on the left side of the skull disclosed no lesion. The patient was later transferred to the Montefiore Hospital. The neurologic findings on admission were: spastic paresis on the right side, with typical signs of disturbance in the pyramidal tract, mild motor aphasia and a mild hemisensory syndrome. Forced grasping was present in the right hand. The patient gradually improved and was able to walk with a spastic hemiparetic gait. The forced grasping gradually became less pronounced, and on August 19 the following note was recorded:

"The forced grasping has diminished greatly in intensity. It can readily be split up into two components: (1) the grasp response to tactile stimulation, which occurs almost immediately when the part is touched, and (2) the tonic

7. Kennard, Margaret A.; Viets, H. R., and Fulton, J. F.: The Syndrome of the Premotor Cortex in Man: Impairment of Skilled Movements, Forced Grasping, Spasticity, and Vasomotor Disturbances, Brain **57**:69, 1934.

innervation response, which occurs when tension is made on the flexor tendon. It is the latter component that has decreased in intensity, for when the patient is in the standing position tactile contact with the hand causes a grasp, but the patient is able to relax this grasp almost immediately despite tension on the flexor tendon. However, if the patient assumes a recumbent posture the tonic innervation component undergoes the following changes: 1. When the patient is in the supine position tactile contact results in a grasp, but relaxation is almost immediately possible despite tension on the flexor tendon. 2. When she is in the left lateral position (with the paretic side uppermost) tactile contact results in a grasp. However, if tension is made on the flexor tendons the patient is unable to relax the grasp so long as the tension is maintained. 3. When she is in the right lateral position (with the paretic side undermost) tactile contact results in a grasp, but relaxation is immediately possible despite tension on the flexor tendon. Tonic influences in the neck and labyrinths are not in evidence."

The patient was discharged greatly improved. She was readmitted on November 9 with the history that during the previous night, while asleep on her left side (with the paretic side uppermost), she had a convulsion involving the right side of the body and face. There were two similar attacks the same night, both occurring when the patient was in the left lateral position. The fourth seizure occurred on the morning that she was admitted to the hospital, while she was sitting up and eating breakfast. After these convulsive seizures the intensity of the grasping was greatly increased over what it had been when she was discharged from the hospital. After a short stay in the hospital, however, it reached the basal level of intensity described previously. During the second period of hospitalization the patient experienced several attacks, all occurring when she was in the reclining position. The forced grasping became more pronounced after each convulsion but reached the basal level within a few days. During the second admission the nature of the tactile stimuli necessary to evoke the grasp was investigated. It was observed, in accordance with the findings of Walshe and Robertson, that whereas the examiner's finger was immediately grasped on contact, no grasping movement followed when a finger of the patient's other hand served as a stimulus. Special care was taken to make sure that the manner of stimulation and the area stimulated were as closely identical as possible; yet in the first instance there was grasping and in the second none.

Comment.—This case illustrates several important points. Not only was it possible to demonstrate that the forced grasping varied with posture in accordance with the postural pattern that has been described, but by means of these postural changes we were able to analyze the reflex into two components, namely, the tactile and the tonic innervation. It was only the tonic innervation component elicited by stretching the flexor tendons of the hand that was influenced by postural changes. The behavior of the tactile component did not fit in with the established concepts of reflex activity. This is further corroborative evidence of the thesis of Walshe and Graeme-Robertson that the tonic innervation component is the only reflex in the clinical phenomenon of forced grasping. It is important to note that with one exception the convulsive seizures occurred while the patient was in the reclining position and that in the first three the observation was made that the patient

was lying on her side, that is, in a lateral posture, with the affected extremity uppermost. Worthy of emphasis is the fact that following each convulsion there was an increase in the intensity of the grasp reflex.

CASE 2.—A. T., a man aged 57, was admitted to the Montefiore Hospital on Sept. 13, 1934, with a history of onset in 1931 of paresthesia and chronic spasms of the left lower extremity. There was gradual progression of weakness in the left extremities, more marked in the lower one. A diagnosis of tumor of the brain was made; an operation was performed, and a parasagittal meningioma was removed. Shortly after the operation forced grasping was noted in the left hand. The grasping reflex was most marked when the patient was lying on his right side, with the left hand uppermost, and least marked when he was lying on his left side. At certain times the reflex could be obtained only when the patient was lying in the right lateral position. The grasping disappeared two weeks after the operation.

Comment.—In this case the reflex at times was elicited only when the patient was placed in the "maximal" position.

CASE 3.—S. G., a woman aged 49, was admitted to the hospital on Oct. 29, 1934, in a semistuporous state, with right hemiplegia and aphasia. Within a week following admission the patient died, and at necropsy a large glioblastoma was noted in the left frontoparietal region. Several hours before death there developed a picture resembling decerebrate rigidity in which forced grasping was present bilaterally. In this state the grasp reflex became accentuated on the uppermost side and diminished on the lowermost when the patient was placed in the lateral position. If the patient was turned to the opposite side the activity was reversed, the limb that was now uppermost having the accentuated grasp reflex and the undermost the depressed one. When the patient was on her back the reflexes were approximately equal.

CASE 4.—H. G., a girl aged 9 years, was seen in the outpatient department of the Montefiore Hospital. The patient's mother refused to have her admitted to the hospital, so that detailed study was not made. All that can be said is that the child had marked hydrocephalus, which dated back to infancy. There was spasticity in all four extremities, with bilateral signs of disturbance in the pyramidal tract. There were definite tonic reflexes of the neck and labyrinths. On testing for the grasp reflex the same phenomenon elicited in the patient in case 3 was demonstrated in this patient. Whenever the patient was placed on her side the grasping became intensified in the uppermost limb and disappeared in the lowermost one. With the patient in the supine position the grasp reflexes were equal on both sides.

Comment.—The patients in cases 3 and 4 exhibited a postural influence on the grasp reflex corresponding to that observed in the experimental bilateral motor and premotor area animals of Fulton.

CASE 5.[8]—A. M., a woman aged 21, was admitted to the Bellevue Hospital with a six year history of tonic and clonic seizures of the right upper extremity and the right side of the face and conjugate movements of the head and eyes to the

8. Dr. Foster Kennedy and Dr. John Scarff gave us permission to report this case.

right. Shortly after their onset the convulsions occurred practically exclusively at night. They came on within a half-hour of the time the patient lay down, whether or not she fell asleep during this period. She volunteered the information that most of the seizures came when she was lying on her left side (placing the affected right hand in the upperlying position). She attempted to abort a seizure by turning to her right side, but this was unsuccessful; nor did lying on this side prevent further seizures. The few seizures that occurred during the day did so only when the patient was lying down. In the several months preceding her admission to the hospital there was an increase in the number of attacks, and the relationship of these to the posture of the patient became less striking than it had been. The majority of them, however, still occurred when she was in the recumbent position. Two types of attacks were described, mild and severe. In the former the fingers, hand and forearm of the right upper extremity begin to feel tight up to the elbow. The tight feelings were followed by clonic movements which lasted up to half a minute. The severe fit began with a sensation of tingling at the xiphoid cartilage which passed to the right shoulder. The right hand then became tight, and finally tonic movement supervened, and the head and eyes turned to the right involuntarily. There was no loss of consciousness in either type of attack. An exploratory craniotomy was performed by Dr. John Scarff, who found a small, discrete cyst of the arachnoid, approximately 1 by 2 cm. By electrical stimulation this was found to be situated about 2 cm. anterior to a point on the motor cortex from which responses of the hand typical of those produced by stimulation of area 4 were elicited. About 2 cm. anterior to the arachnoid cyst and from 2 to 3 cm. closer to the sagittal sinus a point was located the stimulation of which was followed immediately by a violent convulsive seizure. The convolution at this point was thought to be somewhat more red and slightly firmer than the convolutions elsewhere. From this description the subarachnoid cyst can be placed within the premotor zone and the epileptogenic focus either within it or just anterior to it.

Following the operation the seizures occurred on an average of once or twice a night, again tending to come on within a short period after the patient lay down, independent of whether or not sleep supervened. During the day the patient was practically free from seizures, although several did occur while she was in the sitting position.

Comment.—The patient manifested jacksonian seizures of a type suggesting a premotor lesion. This suspicion was confirmed by surgical exploration. For a long time after the disease began and since the operation the convulsions occurred largely when the patient was lying down, whether or not she was asleep.

COMMENT

In the four patients manifesting the symptom of forced grasping which we have described we observed that the phenomenon varied with change in posture. In all the patients the forced grasping varied with changes in position in a manner identical with that which has been described experimentally by Bieber and Fulton [5] and clinically in a patient with "the syndrome of the premotor area" by Kennard, Viets and Fulton.[7] This relationship was such that when the patient occupied

a lateral position the forced grasping was maximal when the affected extremity was uppermost. In case 1 we observed that the alterations in position affected only one portion of the grasp response, the tonic innervation component, or that portion for which the stimulus was stretching the flexor tendons of the hand. The response to tactile stimulation was independent of the posture of the patient and revealed a discrimination to the type of stimuli evoking it that was out of keeping with the reflex activity. These observations corroborate the thesis of Walshe and Robertson that the tonic innervation is the only true reflex component of forced grasping. They are also in accordance with the work of Fulton and his co-workers wherein it was demonstrated that after elimination of the tactile component by anesthetizing the hand the relationship of grasping to the postural pattern remained unchanged.

Case 2 illustrates the clinical importance of placing the patient in the maximal position for eliciting the forced grasping. At times it was impossible to bring out the phenomenon with the patient in any but the maximal position. In cases in which the associated symptoms suggest that forced grasping might be present the reflex should not be considered to be absent unless it cannot be evoked with the patient in this maximal position. Cases 3 and 4 reveal the similarity of what may be observed in the laboratory and in the ward. In respect to forced grasping these patients behaved in a manner identical with that of the bilateral motor and premotor preparations of Fulton. Study of cases 1 and 5 reveals a group of facts which when correlated allow some interesting speculations. In case 1 the association of the onset of the seizures with the recumbent posture and the increase in tensity of the forced grasping after the attack are to be noted. In case 5 there was a similar association of convulsions with posture in a patient with a lesion of the premotor zone.

These observations suggest the following deductions: When a patient assumes the reclining posture a large portion of the body surface becomes stimulated by contact with the supporting surface. This serves as an adequate stimulus for the assumption of postural patterns conditioned by the body-righting reflexes on the body. Ordinarily, in normal persons these patterns can be inhibited by impulses from the premotor areas, as demonstrated by the experiments of Fulton and his co-workers. However, when the premotor area is diseased it becomes functionally insufficient, and after a varying period, during which this functionally insufficient area can inhibit these reflex patterns in the recumbent patient, the zone becomes decompensated. The tonic spasm then replaces the phasic component of the reflex pattern. If a clonic convulsion supervenes it is possible either that an epileptogenic focus in or about the decompensated zone is set off or that the area begins to fire at random, undergoing a total physiologic disintegration. The

increased intensity of the forced grasping after a seizure in case 1 suggests such a disintegration. The fact that the epileptogenic focus is in relation to the physiologic activity of its surrounding area was illustrated in a case brought to our attention by Dr. Eugene Greene. The patient suffered with jacksonian seizures, beginning with turning of the head and eyes to the right. He was able to inhibit the progress of the convulsion by consciously forcing his head and eyes to the left. It is a fact long ago established that when one zone which stands in reciprocal relation to another is stimulated its homolog is inhibited. Thus, by volitionally stimulating the homologous area in the opposite hemisphere this patient reciprocally inhibited the diseased one, causing cessaton of firing from the zone and its epileptogenic focus. That the tonic flexor spasm should occur more frequently when the patient is lying with the affected extremity uppermost is in accordance with these concepts. It is in this position that the greatest demand for inhibition is made on the premotor area.

CONCLUSIONS

1. Forced grasping in man varies with the posture of the subject in a manner similar to that observed in animals with bilateral lesions of the motor and premotor areas, being maximal when the affected extremity is uppermost and minimal when it is undermost.

2. This influence is exerted on the proprioceptive component of the reflex.

3. Postural changes may influence the onset of focal epileptic convulsions, especially when the epileptogenic area is in anatomic relation with the premotor zone.

EFFECT OF ALTERATIONS IN POSTURE ON THE INTRA-ARTERIAL BLOOD PRESSURE IN MAN

I. PRESSURE IN THE CAROTID, BRACHIAL AND FEMORAL ARTERIES IN NORMAL SUBJECTS

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In 1931 two of us [1] described a direct method for measuring the intra-arterial blood pressure in man, together with the results obtained in a series of normal subjects and in persons with arteriosclerosis. In the course of an investigation on the effect of alterations in posture on the venous pressure and the cerebrospinal fluid pressure and on the velocity of blood flow, it was determined that we should study the intra-arterial blood pressure under the same conditions. The method was found to be ideally suited for this investigation, particularly of the pressure in the carotid artery. At first, the effect of alterations in posture on the blood pressure in the carotid artery alone was studied. Later, simultaneous observations of the pressure in the carotid and brachial arteries and in the carotid and femoral arteries were obtained.

The effect of changes in posture on the intra-arterial pressure as measured directly has been studied heretofore only in animals, particularly by Leonard Hill.[2] The effect of alteration of posture on the blood pressure as measured indirectly over the brachial artery in man has been observed by Hill,[3] Ellis,[4] Mortensen,[5] Stephens [6] and others.

From the Division of Research, Boston State Hospital, and the Department of Neurology, Tufts College Medical School.

1. Dameshek, W., and Loman, J.: Direct Intra-Arterial Blood Pressure Readings in Man, Am. J. Physiol. **101**:140 (June) 1932.

2. Hill, L.: The Influence of the Force of Gravity on the Circulation of the Blood, J. Physiol. **18**:15, 1895.

3. Hill, L.: Further Advances in Physiology, New York, Longmans, Green & Co., 1909, p. 43.

4. Ellis, M. E.: Pulse Rate and Blood Pressure Responses of Men to Passive Postural Changes, Am. J. M. Sc. **161**:568, 1921.

5. Mortensen, M. A.: Blood Pressure Reactions to Passive Postural Changes: An Index to Myocardial Efficiency, Am. J. M. Sc. **165**:667 (May) 1923.

6. Stephens, O. Z.: Blood Pressure and Pulse Rate as Influenced by Different Positions of the Body, J. A. M. A. **43**:955 (Oct. 1) 1904.

A study of the arterial pressure by the direct method has a distinct advantage over studies made by the indirect method in that all the various phases of the pressure reactions may be followed during the entire maneuver of a given postural change. A knowledge of the intracranial arterial pressure as reflected in the changing pressures within the carotid artery is important not only from the physiologic standpoint but from the standpoint of information which may be obtained regarding such symptoms as vertigo, syncope and convulsions, in all of which a vascular element may be present.

MATERIAL AND TECHNIC

The patients utilized in this investigation were inmates of the Boston State Hospital. They were all extremely cooperative and were well trained from previous experiments. Most of them had dementia praecox but were otherwise normal. They were placed on a specially designed tipping table,[7] to which they were comfortably strapped by means of a canvas harness which encircled their shoulders, chest and abdomen. The position was further reenforced with strapping across the thighs and below the knees. The feet rested against braces, to which they were securely strapped. The head was held steady by an assistant. With these precautions, the patients could be readily tilted to the completely vertical head-up or head-down position without danger of falling. To eliminate the factor of fear and to insure as much relaxation as possible, the various postural maneuvers were practiced before punctures of the arteries were made. After thorough anesthetization of the skin with procaine hydrochloride at the site of the operation, the common carotid artery was punctured at the level of the thyroid cartilage, where its pulsation is usually readily felt. The internal carotid artery was reached by a special technic described by us in previous papers.[8] It was found that puncture of the common carotid artery was better suited for the purposes of this investigation. In puncturing this vessel, the needle and syringe were held as closely parallel to the skin as possible and maintained in that position throughout the experiment. On withdrawal of the needle, pressure was applied over the site of the puncture for two or three minutes in order to prevent the formation of a hematoma.

A detailed description of the apparatus together with the technic of obtaining direct arterial pressure readings in man has been given in a previous paper.[1] Briefly, the pressure is measured by inserting into an artery an 18 gage needle, which is connected by means of a stopcock to tubing and an aneroid tycos manometer. Parkins[9] utilized this method with trained unanesthetized dogs and

7. Loman, J.; Myerson, A., and Goldman, D.: Effect of Alterations in Posture on the Cerebrospinal Fluid Pressure, Arch. Neurol. & Psychiat. **33**:1279 (June) 1935.

8. Myerson, A.: Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular Vein and the Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927. Myerson, A., and Loman, J.: Internal Jugular Venous Pressure in Man: Its Relationship to Cerebrospinal Fluid and Carotid Arterial Pressures, ibid. **27**:836 (April) 1932.

9. Parkins, W. M.: Observations on Direct Intra-Arterial Determination of Blood Pressure in Trained Unanesthetized Dogs, Am. J. Physiol. **107**:518 (Feb.) 1934.

demonstrated that the readings obtained are practically identical with those given by the standard method, in which a cannula is used. A connecting bulb (15 mm. in diameter) inserted in the system in place of the glass trap originally used was found more satisfactory from the standpoint of delaying the clotting.

Maximal and minimal readings in pressure are obtained. It was pointed out in the earlier paper[1] that the maximal reading corresponds closely to the actual systolic pressure when the pulse pressure is normal (40 mm. of mercury) but approaches the mean pressure when the pulse pressure increased, as in arteriosclerosis. In the text, unless otherwise specified, only the maximal blood pressure readings will be given, although in the charts both maximal and minimal readings are recorded.

TABLE 1.—*Blood Pressure in the Carotid Artery During Slow Alterations in Posture* *

		Head-Up (Vertical)		Head-Down (Vertical)	
Case	Horizontal	Initial Fall	Final Fall	Initial Rise	Final Rise
1	106	56	46	34	24
2	98	40	20	38	32
3	106	38	36	24	24
4	110	24	22	44	40
5	78	24	18	28	28
6	100	22	20	30	30
7	110	30	22	44	38
8	120	32	14	26	24
9	108	30	24	22	20
10	114	44	28	34	24
Average	105	33	23	33	28

* In this and the following tables the blood pressure (systolic) is given in millimeters of mercury.

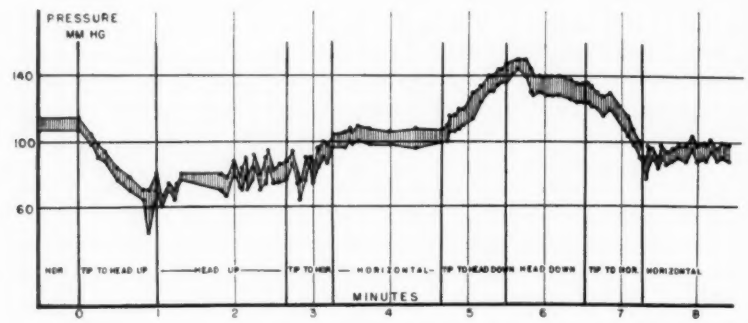

Chart. 1.—Effect on the pressure in the carotid artery. Effect of slow tipping from the horizontal to the vertical head-up and head-down positions. Note the gradual change in pressure and its partial compensatory return toward the horizontal level immediately after the subject reaches either vertical position.

RESULTS

1. The Blood Pressure in the Carotid Artery in the Normal Subject.—RECUMBENT POSITION.—The intracarotid blood pressure was determined in twenty-one subjects whose brachial (indirect) systolic pressure ranged between 100 and 130 mm. of mercury. The readings obtained varied between 78 and 122 mm. of mercury.

TILTING EXPERIMENTS.—The effect of both slow and rapid changes in posture was studied in the same group of normal subjects. The table was first tipped to the vertical head-up position and then to the vertical head-down position.

(*a*) Slow Tipping to the Vertical Head-Up Position: At the completion of the tilting maneuver there was a fall in pressure varying from 22 to 56 mm. of mercury, an average fall for the ten subjects being 33 mm. The intracarotid pressure was usually lowest at about the moment the upright position was reached. Within a few seconds, however, while the upright position was being maintained, a rise in pressure ranging from 2 to 20 mm. usually took place. It was thought that this rise might be a compensatory phenomenon. The net average fall in pressure was 23 mm. of mercury (table 1 and chart 1).

TABLE 2.—*Blood Pressure in the Carotid Artery During Rapid Alterations in Posture*

Case	Horizontal	Head-Up (Vertical)		Head-Down (Vertical)	
		Initial Fall	Final Fall	Initial Rise	Final Rise
1	112	38	34	28	26
2	96	28	12	44	34
3	122	38	22	48	34
4	92	22	12	..	..
5	98	60	24	22	22
6	92	42	2	58	48
7	114	34	26	26	20
8	100	44	24	30	26
9	84	40	26	46	24
10	100	22	18	..	..
11	98	34	26	28	22
Average	103	40	21	36	28

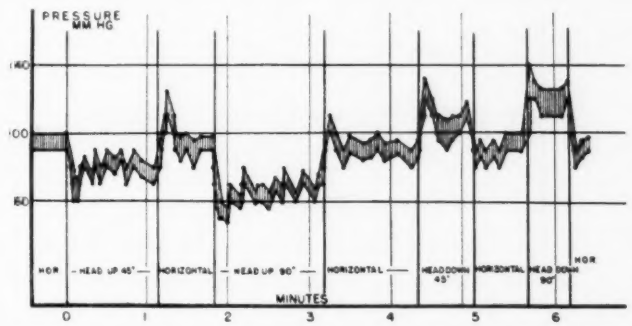

Chart 2.—Effect on the pressure in the carotid artery of rapid tilting from the horizontal to the head-up and head-down positions. The pressure changes rapidly and shows a distinct compensatory reaction.

(*b*) Slow Tipping to the Vertical Head-Down Position: With this shift of posture there was a rise in pressure ranging from 22 to 44 mm. of mercury, with an average increase of 33 mm., a figure identical with the average initial fall in pressure occurring with the shift in the opposite direction. Again, as with the tilting to the head-up position, the greatest change in pressure occurred at about the moment the subject was brought to the vertical head-down position. In this maneuver, however, the compensatory reaction toward the original pressure tended to be slight and was definite in only two instances. The net average rise in pressure was 28 mm. of mercury (table 1 and chart 1).

(*c*) Rapid Tipping to the Vertical Head-Up Position: The fall in intracarotid pressure when rapid tipping was induced ranged from 22 to 58 mm. of mercury, with an average change of 40 mm. This was a somewhat greater change than that which occurred with slow tipping and was accompanied by a corresponding greater compensatory reaction. In seven of the eleven subjects during this compensation the intracarotid pressure rose from 10 to 40 mm. of mercury, whereas with slow tilting, a rise of from 10 to 20 mm. occurred in four instances. The average net fall in pressure, however, was 21 mm. of mercury, a figure practically identical with that obtained with slow tilting (table 2 and chart 2).

TABLE 3.—*Blood Pressures in the Carotid and Brachial Arteries During Slow Alterations of Posture (Simultaneous Measurements)*

	Carotid Artery					Brachial Artery				
		Head-Up (Vertical)		Head-Down (Vertical)			Head-Up (Vertical)		Head-Down (Vertical)	
Case	Horizontal	Initial Fall	Final Fall	Initial Rise	Final Rise	Horizontal	Initial Rise	Final Rise	Initial Fall	Final Fall
1	110	30	24	..	..	100	30	30	..	..
2	100	20	14	..	..	102	22	16	..	..
3	118	16	8	28	24	122	38	38	4	4
4	104	30	14	20	20	110	14	10	20	10
5	144	40	24	26	26	134	4	4	12	12
6	80	28	20	22	22	76	14	14	20	16
Average	109	27	17	24	23	107	20	19	14	8

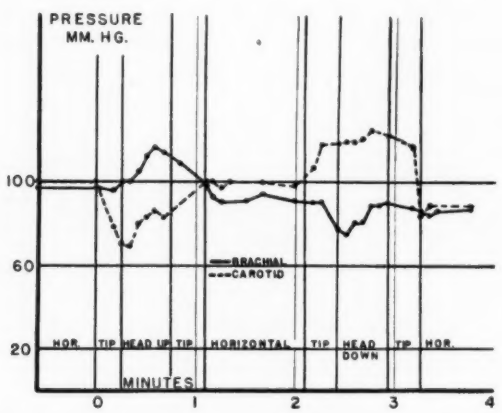

Chart 3.—Simultaneous measurements of pressure in the carotid and brachial arteries after slow vertical tilting. The pressures change in opposite directions. With the head-up position, the pressure in the carotid artery shows a definite compensatory return in pressure, and with the head-down position, the pressure in the brachial artery shows a distinct compensatory reaction.

(*d*) Rapid Tipping to the Vertical Head-Down Position: With this change of posture, there was a rise in pressure in the carotid artery ranging from 22 to 48 mm. of mercury, the average change being 36 mm. In four subjects there was a significant compensatory fall in pressure in comparison with two such reactions in the group who were tipped slowly. Here again, the final net change in pressure (28 mm.) was identical with that which occurred with slow tilting (table 2 and chart 2).

2. Simultaneous Intracarotid and Intrabrachial Blood Pressure.—The pressure in the carotid and brachial arteries was simultaneously measured in six subjects. With the patient in the prone position and the level of the two vessels as nearly equal as possible, the pressures within the two arteries were identical.

(*a*) Slow Tipping to the Vertical Head-Up Position: With this maneuver the fall in pressure in the carotid artery ranged in the six subjects from 12 to 40 mm. of mercury, with an average of 27 mm. During the maneuver the pressure in the brachial artery rose from 4 to 38 mm., the average rise being 20 mm. The maximum pressure in the brachial artery did not always occur at the moment the minimum

TABLE 4.—*Blood Pressure in the Carotid and Femoral Arteries During Slow Alterations in Posture (Simultaneous Measurements)*

	Carotid Artery					Femoral Artery				
		Head-Up (Vertical)		Head-Down (Vertical)			Head-Up (Vertical)		Head-Down (Vertical)	
Case	Horizontal	Initial Fall	Final Fall	Initial Rise	Final Rise	Horizontal	Initial Rise	Final Rise	Initial Fall	Final Fall
1	108	24	18	..	..	108	44	44	..	..
2	126	26	22	20	16	126	34	18	34	24
3	102	28	20	..	..	102	36	36	..	..
4	114	30	15	..	..	114	40	40	..	..
5	110	36	18	26	26	108	42	42	22	14
6	92	24	20	26	26	102	42	42	42	26
7	118	48	30	..	..	118	24	2	..	..
Average	110	31	20	24	23	111	39	31	33	21

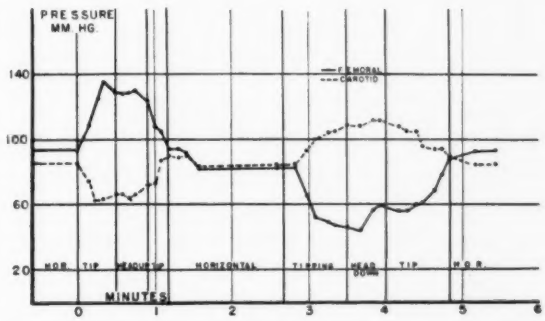

Chart 4.—Simultaneous measurements of pressure in the carotid and femoral arteries. The pressure in the femoral artery with the patient in the head-down position shows the most distinct compensatory reaction.

pressure in the carotid artery was registered. In every instance there was evidence of some compensatory rise in the pressure in the carotid artery, while it was absent in every instance but one in the pressure in the brachial artery (table 3 and chart 3).

(*b*) Slow Tipping to the Vertical Head-Down Position: This maneuver was done in four cases. In these the rise in pressure in the carotid artery ranged from 18 to 28 mm. of mercury, while the fall in pressure in the brachial artery varied from 4 to 20 mm. There was practically no compensatory reaction of the pressure in the carotid artery, although the pressure in the brachial artery showed some degree of change in two subjects (table 3 and chart 3).

3. Simultaneous Intracarotid and Intrafemoral Arterial Blood Pressure.—The blood pressure within the carotid and femoral arteries was compared in seven persons simultaneously. When the subjects were in the horizontal position, the blood pressures were equal or practically equal in every instance.

(*a*) Slow Tipping to the Vertical Head-Up Position: The maximum rise in pressure in the femoral artery was usually obtained at the moment the pressure in the carotid artery reached its lowest reading. The rise in pressure in the femoral artery ranged from 24 to 44 mm. of mercury, while the fall in pressure in the carotid artery varied from 24 to 48 mm., an average change of 39 and 31 mm., respectively. On the whole, the compensatory rise in pressure in the carotid artery was greater than the compensatory fall in pressure in the femoral artery (table 4 and chart 4).

(*b*) Slow Tipping to the Vertical Head-Down Position: This maneuver was performed in three instances. The pressure in the carotid artery rose 20 mm., 26 mm. and 26 mm., respectively, while the pressure in the femoral artery fell 34 mm., 22 mm. and 42 mm., respectively. The compensatory change in pressure in the carotid artery was present only slightly in one subject, although in the case of the pressure in the femoral artery it was observed in some degree in all three persons studied.

COMMENT

That a change in posture from the horizontal to the upright position effects a fall in the pressure in the carotid artery and that the opposite maneuver brings about a rise was noted in animals about forty years ago by Leonard Hill.[2] Hill,[2] Hill and Barnard,[10] Ellis,[4] Mortensen,[5] Stephens [6] and others have also noted the changes occurring in the blood pressure in the brachial artery (indirect method) during the same maneuvers. Hill pointed out that there are two important forces involved in the alteration of arterial pressure during changes in posture.

1. *The Force of Gravity.*—As noted in the foregoing experiments, the change in pressure in the carotid artery that occurs when subjects with normal vascular systems are tipped from the horizontal to the vertical position varies from 20 to 60 mm. of mercury. Similar changes of pressure in the opposite direction occur in the pressures in the brachial and femoral arteries during the maneuvers. Such alterations in pressure could not ordinarily be correlated with any fixed distance, for example, that from the heart to the site of arterial puncture. This lack of correlation indicates that the change in pressure cannot be due to the force of gravity alone but must, as Hill has clearly shown, involve another component, which varies from person to person.

2. *The Dynamic or Vasomotor Component.*—From his experiments on animals, Hill [2] offered the explanation that the changes in pressure effected by the force of gravity are altered as follows: With the subject in the upright position, compensation for the fall in pressure in the

10. Hill, L., and Barnard, H.: The Influence of the Force of Gravity on the Circulation: II, J. Physiol. **21**:323, 1897.

carotid artery is brought about through splanchnic vasoconstriction, associated in some cases with cardiac acceleration; with the subject in the opposite position, splanchnic vasodilatation occurs and is accompanied by cardiac inhibition. These changes in pulse rate have also been observed by Ellis [4] and Stephens.[6] Hill and Barnard [10] also indicated, from their experiments with animals, the rôle played by the respiratory system in aiding to sustain the blood pressure during alterations of posture. These authors pointed out that although the splanchnic vasomotor system is by itself amply sufficient to compensate for the hydrostatic effect of gravity, when this mechanism is destroyed the respiratory pump aids in the maintenance of the circulation. When both these systems are abolished, circulation in the feet-down position becomes impossible.

Since Hill denied the existence of a cerebral vasomotor system, he omitted its implication in his explanation of the compensatory mechanism. Although the observations of Forbes and Wolff [11] strongly indicate the existence of vasomotor control of the pial vessels, we believe that a central vasomotor mechanism plays a subsidiary rôle in protecting the brain from marked variations in pressure during alterations of posture. That the splanchnic area is much more important in the control of blood pressure, including that of the cerebral arteries, will be indicated in a subsequent report. At present it appears probable that as long as the general arterial pressure is maintained above a certain level, the cerebral circulation does not suffer appreciably when the body is tilted to the upright position.

The data in the foregoing experiments indicate that during a slow shift to the vertical head-up position the compensatory mechanism begins to act soon enough to prevent the maximal fall due to gravity alone. During rapid shifting, however, there is no time for this to occur, so that, while the final level in pressure is the same, a greater fall and a correspondingly greater rise have taken place.

Whatever the exact mechanism which prevents marked variations in pressure from occurring in the cerebral arteries, it seems necessary for the preservation of an adequate cerebral circulation that the systemic arteries, as well as those of the brain, maintain at all times a good tone. Impairment of this quality, as by arteriosclerosis, together with alterations in posture, may place so great a strain on the cerebral vascular system as to cause recognizable clinical symptoms. Some of the conditions under which this may occur will be the subject of a subsequent paper.

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11. Forbes, H. S., and Wolff, H. G.: Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

SUMMARY AND CONCLUSIONS

The effect of alterations in posture on the arterial blood pressure within the carotid, femoral and brachial arteries was studied in a group of human subjects with apparently normal vascular systems. Observations of the pressure in the carotid artery alone and simultaneous observations of the pressure in the carotid and brachial and in the carotid and femoral arteries were made.

The intracarotid arterial pressure dropped from 22 to 60 mm. of cury when the patient was shifted to the vertical head-down position, while simultaneously the pressure in the brachial artery rose from 4 to 22 mm. of mercury, and the pressure in the femoral artery rose from 22 to 40 mm. of mercury. The initial drop in the pressure in the carotid artery was usually followed by a compensatory rise in pressure of from 10 to 20 mm. of mercury, the change being greatest when rapid change in posture took place.

The pressure in the carotid artery rose from 18 to 36 mm. of mercury when the patient was shifted to the vertical head-down position, while simultaneously the pressure in the brachial artery fell from 4 to 22 mm. of mercury and the pressure in the femoral artery fell from 22 to 40 mm. of mercury. The compensatory reactions were much less striking than with the shift of posture in the opposite direction.

The significance of these observations together with the possible mechanisms of the compensatory reactions in blood pressure is discussed.

The subject with a normal vascular system overcomes by various compensating mechanisms (splanchnic, vasomotor, etc.) the possibly deleterious effects of the force of gravity.

EFFECT OF ALTERATIONS IN POSTURE ON THE INTRA-ARTERIAL BLOOD PRESSURE IN MAN

II. PRESSURE IN THE CAROTID ARTERY IN ARTERIOSCLEROSIS, DURING SYNCOPE AND AFTER THE USE OF VASODILATOR DRUGS

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ABRAHAM MYERSON, M.D.

AND

DAVID GOLDMAN, B.A.

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In a previous communication [1] we presented data on the behavior of the blood pressure in the carotid artery in man during alterations in posture. Observations were made on a group of subjects with normal circulation and blood pressure, the blood pressure being measured by the use of a simple technic previously described by two of us.[2] The present study deals with observations on the effects of alteration in posture in persons with certain abnormal conditions. The intracarotid arterial pressure was studied: (1) in a small group of old men with various degrees of hypertension and arteriosclerosis, (2) in a subject undergoing an attack of syncope, and (3) in a group of subjects with normal cardiovascular systems to whom vasodilator drugs were administered. The technic of the experiment has been described in the aforementioned communication.

RESULTS

1. *Pressure in the Carotid Artery in Persons with Arteriosclerosis* (table 1 and chart 1).—Six subjects in whom the (indirect) systolic pressure in the brachial artery ranged from 180 mm. to 218 mm. of mercury were studied. The pressures (direct) in the carotid artery measured in the supine position ranged from 110 to 180 mm.

(*a*) Effect of slow shift in posture from the supine to the upright position: This maneuver caused a fall in pressure ranging from 26 to 60 mm. of mercury,

From the Division of Research, Boston State Hospital, and the Department of Neurology, Tufts College Medical School.

1. Loman, J.; Dameshek, W.; Myerson, A., and Goldman, D.: Effect of Alterations in Posture on the Blood Pressure in Man: I. Pressure in the Carotid, Brachial and Femoral Arteries, Arch. Neurol. & Psychiat., to be published.

2. Dameshek, W., and Loman, J.: Direct Intra-Arterial Blood Pressure Readings in Man, Am. J. Physiol. **101**:140 (June) 1932.

a range similar to that previously observed in the group with normal cardiovascular systems.[1] However, no secondary rise in pressure took place. On the contrary, in four persons, once the upright position had been reached, the pressure continued to fall. In another there was no difference between the initial and the final pressure in an upright position. In the other subject the pressure was so irregular (auricular extrasystoles) that it was impossible to gage any compensatory response. It was interesting also to observe a decrease of the pulse pressure when the subject was tilted to the upright position. Finally, repetition of head-up tilting caused a steady fall in pressure associated with a marked decrease of the pulse pressure. The subject was returned to the horizontal position the moment the pressure had reached the level of 70 mm. of mercury.

(*b*) Effect of slow shift in posture from the supine to the head-down position: With this shift of posture, the pressure in the carotid artery rose from 10 mm. to 60 mm. In only two instances was there any significant compensatory fall (10 mm.) in pressure.

TABLE 1.—*Pressure in the Carotid Artery* * *in Persons with Arteriosclerosis During Slow Tilting*

Case	Horizontal	Head-Up (Vertical)		Head-Down (Vertical)	
		Initial Fall	Final Fall	Initial Rise	Final Rise
1	176	56	62	24	14
2	110	60	60	60	50
3	136	26	36	28	22
4	180	30	40	10	10
5	160	30	50	28	20
6	140	36	36	34	30
Average	151	40	47	31	28

* In this and the following tables the pressure is given in millimeters of mercury.

2. *Pressure in the Carotid Artery During Syncope* (chart 2).—One subject, whose pressure was 98 mm. of mercury when in the supine position, was tilted suddenly without warning to the upright position. When the 45 degree position was reached, the pressure in the carotid artery had fallen to 78 mm. of mercury. With the subject held in that position the pressure continued to fall, so that when fifty seconds had elapsed it was 28 mm., a total decrease of 70 mm. From the twentieth to the fiftieth second the oscillations of the manometer were barely perceptible. In the meantime the subject became very pale; large beads of perspiration broke out on his face, and he fainted. He was immediately returned to the horizontal position, during which time the pressure returned to 40 mm. It then gradually increased to its original level (98 mm.) in a period of two minutes.

Two days later the same procedure was repeated on this subject but he was fully prepared and was not surprised or frightened as in the first experiment. He now reacted normally, the fall in pressure being only 22 mm. (chart 3).

3. *Reactions of the Pressure in the Carotid Artery to Vasodilator Drugs* (tables 2 and 3).—Amyl nitrite, sodium nitrite and histamine were administered to several subjects whose blood pressures were within normal limits.

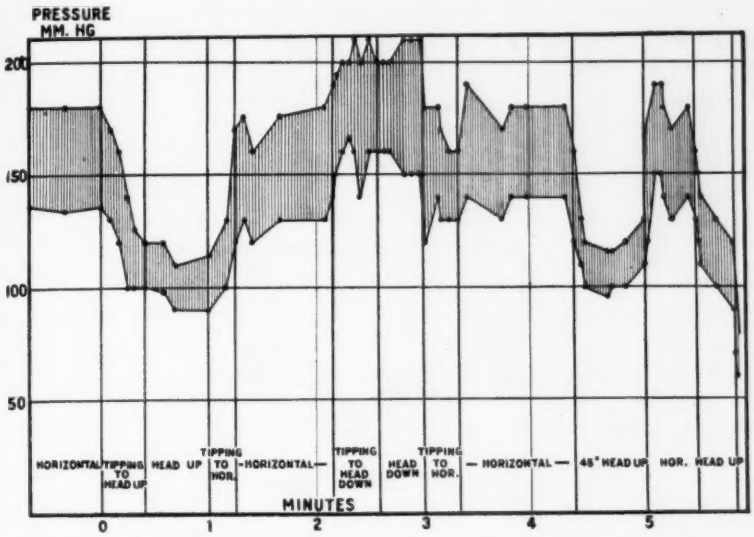

Chart 1.—Effect of alteration in posture on the pressure in the carotid artery in a subject with arteriosclerosis and auricular extrasystoles. Note that repetition of tilting to an upright position resulted in a drop of pressure to 70 mm. of mercury.

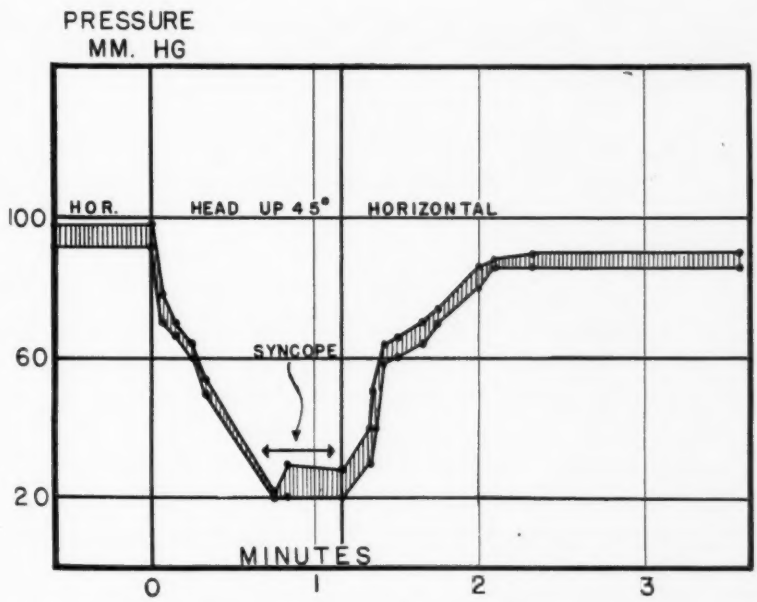

Chart 2.—Effect of sudden unexpected tilting to an upright position on the pressure in the carotid artery. Syncope occurred after fifty seconds.

(*a*) Amyl Nitrite: This drug was inhaled by four subjects. The behavior of the pressure in the carotid artery before and after administration of the drug may be noted in table 2. When the drug had become effective, as indicated by a fall in pressure, the subjects were tilted rapidly to the vertical head-up position. No consistent differences in behavior of the pressure in the carotid artery before or after the administration of the drug were noted.

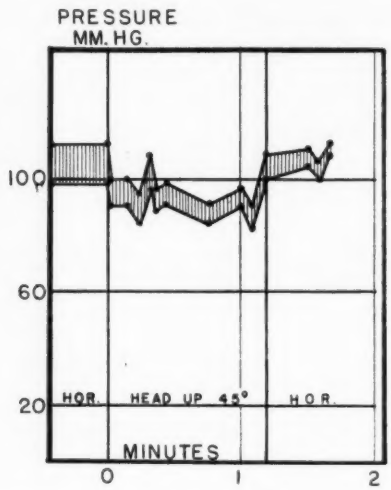

Chart 3.—Normal response in the same subject whose record is shown in chart 2. This experiment was performed two days later, and the subject was not surprised or frightened.

TABLE 2.—*Pressure in the Carotid Artery During Rapid Tilting to the Head-Up Position Before and After Administration of Nitrite*

	Before					After				
		Head-Up					Head-Up			
Case	Horizontal	Initial Pressure	Initial Fall	Final Pressure	Final Fall	Horizontal	Initial Pressure	Initial Fall	Final Pressure	Final Fall
1*	82	40	42	54	28	84	46	38	22	62
2	100	56	44	74	26	94	60	34	66	28
3	100	66	34	70	30	70	56	16	80	10
4	96	62	34	66	30	96	68	30	76	22
5	122	80	42	90	32	90	50	40	96	6
Average	100	61	39	71	29	87	56	31	68	25

* Sodium nitrite (2 grains subcutaneously). The other subjects were given amyl nitrite by inhalation.

(*b*) Sodium Nitrite (table 2, case 1, and chart 4): One subject was given a subcutaneous injection of 2 grains of sodium nitrite after his normal reaction to changes in posture had been observed. Before administration of the drug, rapid tilting to the upright position resulted in a fall of pressure in the carotid artery

of 42 mm. of mercury and a compensatory rise of 14 mm. Three minutes and forty seconds after the injection of the drug, rapid tilting to the upright position was again done. Within two seconds from the beginning of this maneuver, the pressure in the carotid artery had fallen 54 mm. (from 84 to 30 mm.). Only a slight secondary rise took place, which was followed by a still greater drop in pressure to 22 mm. During the latter period the subject became very pale, his pulse was feeble and he appeared to be on the verge of syncope. When he was restored to the horizontal position the pulse became stronger, and within ninety seconds the pressure gradually rose to its original level.

(*c*) Histamine (table 3 and chart 5): A similar procedure was carried out with histamine hydrochloride (0.6 cc. of a 1:1,000 solution injected intramuscularly) on six subjects. Before administration of the drug the fall in pressure in the carotid artery during rapid tilting to the upright position ranged from 32 to 52 mm., and the secondary rise was of moderate degree in five of the six subjects. When marked flushing of the face occurred, rapid tilting was repeated.

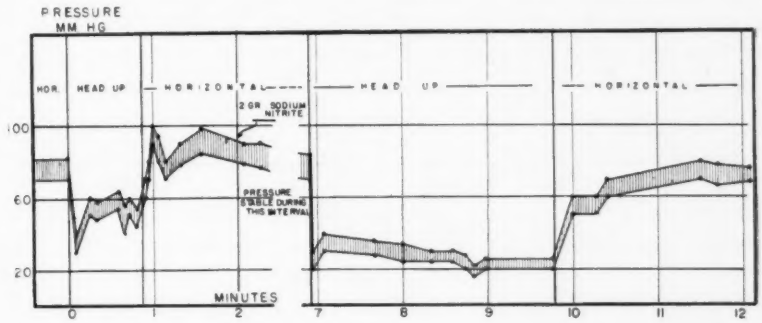

Chart 4.—Effect of sodium nitrite (2 grains subcutaneously) on the pressure in the carotid artery during tilting to the head-up position. The subject was practically in syncope.

The fall of the pressure was then from 22 to 38 mm., on the whole a narrower range than that occurring before the drug had been given, although the actual pressure with the subject in an upright position in every case was now distinctly lower. More significant, however, was the difference in the secondary responses. Whereas prior to the administration of the histamine there was a secondary rise in pressure, after the injection of the drug there was in three persons a secondary fall in pressure (table 3, cases 1, 2 and 4).

One of the reactions to histamine deserves particular comment (table 3, case 1, and chart 5). In this case the pressure in the carotid artery with the subject in the supine position was 92 mm. of mercury. Rapid tilting to the upright position resulted in a striking fall in pressure, of 52 mm. of mercury, with a secondary rise of 16 mm. One minute after administration of the histamine, when the pressure in the carotid artery was 56 mm., rapid tilting was again done. The initial pressure with the subject in an upright position was now 26 mm. The pressure continued to fall rapidly, so that fifteen seconds from the beginning of the tilting maneuver the pressure registered only 14 mm. of mercury. At this

point there developed clonic movements of the head, arms and legs. Rapid resumption of the supine position resulted in a cessation of these abnormal movements and a rise of pressure in the carotid artery to 70 mm. of mercury within fifteen seconds.

TABLE 3.—*Pressure in the Carotid Artery During Rapid Tilting to the Vertical Head-Up Position Before and After Administration of Histamine*

	Before					After				
		Head-Up					Head-Up			
Case	Horizontal	Initial Pressure	Initial Fall	Final Pressure	Final Fall	Horizontal	Initial Pressure	Initial Fall	Final Pressure	Final Fall
1	92	40	52	56	36	56	26	30	12	44
2	104	66	38	88	16	70	48	22	44	26
3	122	74	48	98	24	96	58	38	74	22
4	100	66	34	70	30	70	40	30	36	34
5	104	72	32	84	20	90	54	36	68	22
6	100	60	40	84	16	70	32	38	54	16
Average	104	63	41	80	24	75	43	32	48	27

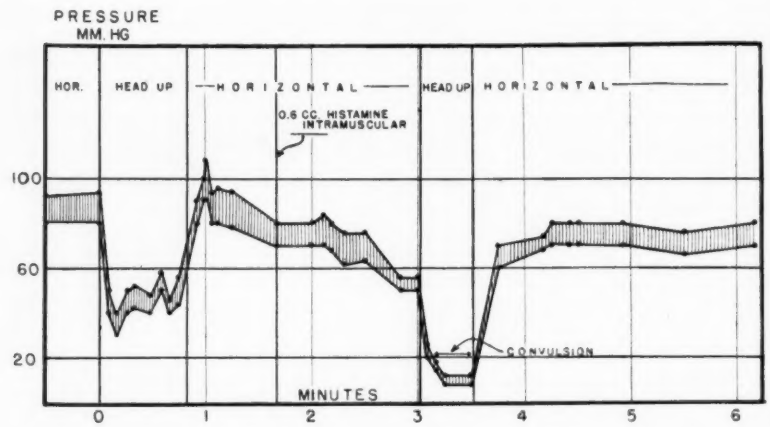

Chart 5.—Effect of histamine hydrochloride (0.6 cc. of a 1:1,000 solution injected intramuscularly) on the pressure in the carotid artery during tilting to an upright position. The patient was returned to a supine position when convulsive movements began.

COMMENT

We previously discussed [1] the mechanism by which the vascular system probably adjusts itself to alterations in posture. In the change from the horizontal to the upright position, it seems necessary that the arteries maintain good contractility, since impairment or loss of this function would result in so great a fall in cerebral arterial pressure that the cerebral circulation would be placed at a definite disadvantage.

When the normal subject was tilted to the upright position, a fall in pressure in the carotid artery took place, followed usually by a secondary rise or a maintenance of the initial change in pressure.

In four of six subjects with arteriosclerosis this normal type of reaction appeared to be lacking. In all six subjects the pressure in the carotid artery showed no tendency to adjust itself, and in four it actually fell to a still lower level after reaching the initial level with the subject in an upright position. This reaction is probably an expression of either general or local arteriosclerotic changes which have impaired the normal elasticity of the vessel walls.

Failure of the compensatory mechanism reaches its acme when, for one reason or another, there is paralysis of the vasomotor system. As Hill [3] stated, when the power of compensation becomes impaired as a result of paralysis of the splanchnic vasoconstrictor nerves due to severe operative procedures, injuries to the spinal cord, asphyxia or poisons, such as chloroform or curare, compensation in the upright position becomes abolished. Under the pull of gravity the blood pressure falls tremendously, the blood collecting in the veins of the splanchnic area. Analogous situations may be produced by fear and by the administration of vasodilator drugs together with the added factor of change in posture from the horizontal to the upright position. The cerebral arterial pressure falls to a very low level, and with the associated drop in blood flow [4] a relative anoxemia with resulting syncope may develop. This is well brought out in the experiments cited.

Clinically, the importance of the effect of posture on the cerebral vascular system has been recognized for many years. Thus, in 1826, Piorry [5] cited the case of a patient who had become unconscious and was being kept in the sitting position. Piorry revived the patient by placing him in the horizontal position. He stressed the great effect of the force of gravity on the circulation, particularly in patients weakened from any cause. A similar experience was reported by von Basedow,[6] who observed that syncope was produced in a patient who had been bled for apoplexy when he was put in the upright position and that it was abolished in the horizontal position. Hall [7] found that syncope could be reinduced in dogs which had recovered from severe hemorrhage if they were placed in the vertical tail-down position and that immediate

3. Hill, L.: The Influence of the Force of Gravity on the Circulation of the Blood, J. Physiol. **18**:15, 1895.

4. Gibbs, F. A.; Loman, J., and Myerson, A.: The Effect of Postural Changes upon the Blood Flow in the Internal Jugular Vein, unpublished data.

5. Piorry, P. A.: Recherches sur l'influence de la pesanteur sur le cours du sang, Arch. gén. de méd. **12**:527, 1826.

6. von Basedow: Einfluss der Gravitation auf die Blutcirculation, Wchnschr. f. d. ges. Heilk., 1938, p. 689.

7. Hall, M.: Experimental Investigation of the Effects of Loss of Blood, Med.-Chir. Tr. **17**:250, 1831-1832.

relief was afforded when the position was reversed. Similar observations were made by Hill.[3]

It is obvious from the foregoing experimental data that the brain functions adequately until the cerebral arterial pressure falls to a surprisingly low level. This level appears to be in the neighborhood of 20 mm. of mercury—a loss of approximately 75 per cent of the original pressure. These figures may be compared with the percentage fall in oxygen saturation which occurs in syncope as observed by Gibbs and Lennox. These authors found that syncope was induced when the oxygen saturation of the blood in the internal jugular vein fell to 28 per cent.[8]

When the position of the body is altered from the horizontal to the head-down position, it is necessary that the brain be protected through the powerful contractility of the arteries against any great increase in blood pressure. In this position, however, since the cerebral blood flow becomes coincidentally increased,[4] the factor of cerebral anoxemia does not enter.

SUMMARY AND CONCLUSIONS

Observations on the intracarotid arterial pressure during extreme alterations in posture were made in a group of subjects (1) with arteriosclerosis, (2) during syncope and (3) after the use of vasodilator drugs. Experiments on the effect of alterations in posture in a group of normal subjects have been reported in a previous communication.

In subjects with severe arteriosclerosis, the pressure in the carotid artery when the subject is tilted to the upright position shows no tendency to maintain itself or to return to a higher level after the initial drop. In fact, it may show a secondary fall. This differs from the normal reaction, in which some compensatory rise usually takes place.

A subject with normal circulation, when suddenly tilted to the upright position, fainted, the blood pressure in the carotid artery falling to 28 mm. of mercury. This was probably the result of introducing the added stimuli of fear and surprise to the vascular strain of tilting. Other observations of the pressure in the carotid artery were made after the use of vasodilator drugs, which sometimes cause an extreme drop in pressure, resulting in syncope or a convulsion.

The following conclusions may be drawn:

1. The reaction to alterations in posture in subjects with arteriosclerosis often is defective.

2. Syncope may occur when the blood pressure in the carotid artery drops to a level of about 20 to 30 mm. of mercury.

3. Vasodilator drugs appear to destroy the normal compensatory reaction, which is probably a function of the vasomotor system.

8. Gibbs, F. A., and Lennox, W. G.: Personal communications to the authors.

FUNCTIONAL AND HISTOLOGIC STUDIES OF SOMATIC AND AUTONOMIC NERVES OF MAN

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During the past seven years it has been possible at various times to secure human nerves fresh enough for physiologic and histologic studies similar to those which we carried out on animal nerves. The present paper summarizes these results and compares the observations on human nerves to those on the corresponding nerves of laboratory animals. References to other publications on this subject have been included in our previous papers reporting investigations on animal nerves, to which the reader is referred as occasion arises. Most of the specimens were secured under conditions as favorable as are possible with laboratory animals, while with others some delay was unavoidable. Material taken for biopsy or at operation could be utilized within fifteen minutes, while with certain material obtained at coroner's autopsies on persons who died by violence about an hour elapsed before the action potentials of the nerves were recorded. This resulted in a variable measure of depression, which must be taken into account in the interpretation of the results involving quantitative data. With nerves to the skin and muscle, stimulation was often first carried out in the body, and the thresholds for, or changes in, bodily function were noted. After the nerves were removed from the body, the action potentials were studied. This permitted a correlation between function in the body and the form of potential of the nerve by a comparison of the thresholds. As correlations were also established between potential maxima and the maxima for size distribution of the fibers, it has been possible to associate specific functions in the body with specific groups of fibers. While

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the material studied did not include nerves from all regions of the body, a sufficient number of typical somatic and autonomic nerves is reported on to serve as a basis for comparison with the nerves of animals. In this paper such comparisons take a prominent part because of their importance in comparative physiology and anatomy. It may be stated that the results indicate definitely that the nerves of man are functionally and histologically closely similar to the nerves of other mammals. There is a striking separation of all nerve fibers of the vertebrate into two great divisions, one group with fast properties characteristic of somatic nerve fibers and the other with slow properties characteristic of autonomic fibers. Both types, however, perform both sensory and motor functions.

MATERIAL AND METHODS

The human nerves reported on included a typical cutaneous nerve, a typical nerve to muscle, the phrenic nerve, the genitofemoral nerve, the vagus nerve, the cervical portion of the sympathetic trunk and the abdominal portion of the sympathetic chain. Similar nerves have been studied functionally and histologically in other mammals, such as the monkey, dog, cat and rabbit (Bishop and Heinbecker[1] and Bishop, Heinbecker and O'Leary[2]). Many of them have also been investigated in the frog, turtle and lobster and Limulus polyphemus.

For the functional analyses the cathode ray oscillographic technic has been used throughout. For the benefit of persons not primarily physiologists the method is briefly described. The cathode ray oscillograph is generally employed for electrical measurements, but it has been recently applied to physiologic studies. It is a thermionic vacuum tube of a type in which a beam of electrons is projected on a fluorescent screen painted on the end of the tube. The electron beam on its course to the screen passes between two pairs of plates set at right angles to each other. A potential applied to the vertical pair of plates deflects the beam in the horizontal plane, and the focused electrons move across the screen as a line. The speed of this movement across the screen can be controlled and measured. The line serves the same purpose as a base line in a kymographic record. By means of a circuit breaker or double key a stimulus may be synchronized with any point in this deflection. This stimulus, together with the resultant action potential from the nerve, is applied to the other pair of plates, which causes a deflection of the electron beam at right angles to the base line.

It is known that when a nerve fiber becomes active there is a change of potential at the site of activity. This activity is propagated along the nerve fiber. Recording electrodes placed on the nerve serve to convey the change of potential of activity to the amplifier-oscillograph combination and cause a deflection of the electron beam. As different fibers within a complex nerve trunk have different rates of conduction, it is readily understood that when a group of fibers is activated by an electrical stimulus and the activity is propagated along the axons, the fibers in which the propagation is most rapid will produce a change in the recording

1. Bishop, G. H., and Heinbecker, P.: Am. J. Physiol. **94**:176, 1930.

2. Bishop, G. H.; Heinbecker, P., and O'Leary, J. L.: Nerve Degeneration Accompanying Experimental Poliomyelitis, Arch. Neurol. & Psychiat. **27**:1070 (May) 1932.

electrodes before the more slowly conducting axons.[2a] As a consequence, from a complex nerve trunk the complete conducted action potential consists of a series of elevations if the distribution of fibers is not uniform. By correlation of the recorded potential with the number and size of the nerve fibers, as revealed in sections stained with osmic acid, it has been possible to correlate with each of the various waves a specific group of fibers which was essentially responsible for its production. The fiber groups have also different thresholds, so that by increasing gradually the strength of the stimulating current, one wave after another may be elicited and by observing the effect in the intact animal as each wave appears on the oscillograph, it is possible to determine the function of the various fiber groups. Besides responses to electrical stimuli, spontaneous responses can be recorded.

On completion of the various functional studies, the nerves were studied histologically by the osmic acid and silver-pyridine technics. With the former method the nerves were stretched slightly on glass rods and fixed by immerson in 1 per cent osmic acid for from twelve to twenty-four hours. After they were washed for twenty-four hours, they were dehydrated and embedded in paraffin or doubly embedded in pyroxylin and paraffin according to the technic of Stieve (Romeis [3]). Sections 5 microns in thickness were cut from the lower end of the nerve. The lower segments were drawn through pieces of similar length of the spinal cord of the cat (Ranson and Davenport [4]), fixed in ammoniated alcohol and subjected to the Ranson method of silver impregnation. Cross-sections 5 microns in thickness were cut from the upper end. The fibers in cross-sections of the various nerves stained with silver and osmic acid were counted. The diameters of the myelinated fibers were measured, and their number was plotted against the size of the fibers.

It seemed desirable to plot these data in a form that would make them directly comparable to the electrical records of the action currents of the nerves, since many of the pertinent physiologic data on nerve function have been referred to the potential picture. For the graphs shown in charts 1 to 9 the data were handled in the following manner: Both the threshold and the conduction time tend to vary as the reciprocal of the diameter of the fiber. A chart was constructed with circles drawn to represent fibers of various sizes, so chosen that the reciprocals of their diameter differed by equal amounts for simplicity in plotting. This was photographed on a process plate at such a reduction that the circles could be compared with sections of nerve fibers magnified 500 or 1,000 times, which were either photographed or projected in a dark hood. Millimeters on the glass measuring scale were read as microns of fiber diameter, and the fibers were counted in groups on the basis of size by comparing each fiber with the nearest measuring circle. Since on this reciprocal scale equal space intervals subtend smaller size intervals as the size decreases, the space intervals for the small fiber range were increased by multiples of the space intervals for the large fiber range to correspond to a measurable difference in size. The sizes measured were laid off on the base line of the chart, and each size was taken to include fibers of a range from one-half the distance to the next larger size to one-half the distance to the

2a. Gasser, H. S., and Erlanger, J.: Rôle Played by Sizes of the Constituent Fibers of a Nerve Trunk in Determining the Form of Its Action Potential Wave, Am. J. Physiol **80**:522, 1927.

3. Romeis, B.: Taschenbuch zur mikroskopischen Technik, ed. 12, Munich, R. Oldenbourg, 1928.

4. Ranson, S. W., and Davenport, H. K.: Am. J. Anat. **48**:331, 1931.

next smaller size. The total number of fibers in a group was then divided by the size range (distance on the x axis) subtended by this group to give the amplitude of a rectangle the area of which represented the number of fibers in this size group. The step curve is therefore the actual number curve as measured against the reciprocal of diameter.

To obtain the approximate curve for area of fibers plotted against reciprocal of fiber size for comparison, for instance, with a plot of area of action potential against strength of stimulus, the ordinate of each rectangle was multiplied by the square of the average fiber diameter and was plotted over the appropriate fiber size. This gave the points for the continuous curves drawn on the charts.

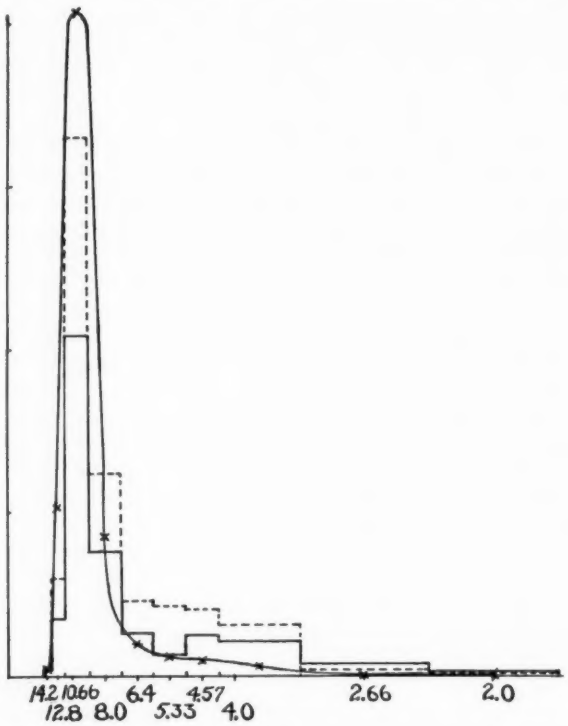

Chart 1.—Graph for two fascicles of the motor nerve to the median head of the gastrocnemius muscle, taken at biopsy, showing the number of myelinated fibers (rectangular curves) and the total areas of the fibers of both fascicles (smooth curve) plotted against the reciprocal of diameter. In this chart and in charts 3, 5, 6, 7, 8 and 9 the reciprocal of the fiber diameter is measured on the x axis. The curve for one fascicle shows the trace of a division into two groups and the curve for the other, a continuous distribution. The nerve to the gastrocnemius muscle of the cat shows uniformly the first type of distribution (bimodal), while after section of the motor roots the remaining sensory component has the second (continuous) type of distribution, the bimodal character of the curve being accentuated after section of the dorsal roots. The characters of the curves for these two fascicles are presumably a function of the relative numbers of their sensory and motor fibers. The curve for the sum of the two would be closely similar to that for the nerve of the cat.

It should be noted in comparison, for instance, with similar curves plotted directly against fiber diameter instead of against its reciprocal that our manner of plotting alters the apparent distribution but does not greatly alter the size position of the maxima and minima, although it does alter the relative amplitudes of the elevations as drawn. The curves for area are in some cases so nearly like the plots for area of action potential against strength of stimulus that they may be substituted for them; in fact, if the nerve is large, so that not all the fibers are equally accessible to the stimulating current, there is almost certainly a greater error in the recording of action currents than in the counting of fibers. Further, when the picture is that of a potential of large area followed by one of small area, our recording apparatus may be deflected so far by the first potential at a sensitivity that would record the second that an instrumental distortion is introduced into the measurement of the smaller area, which leaves the anatomic measurement in certain respects the more reliable index of the composition of the nerve.

NOMENCLATURE

The nomenclature employed in this presentation is one which we have adopted in other studies on analysis of nerves (Bishop and Heinbecker [1]). The four major potential maxima or waves encountered in the study of nerve trunks from the various parts of the peripheral nervous system have been labeled A, B_1, B_2 and C. The A wave is derived from the larger myelinated fibers present in a mixed nerve ranging in size approximately from 18 microns (in the human subject) to 6 microns. The B_1 wave is derived from myelinated somatic fibers approximately from 6 to 2 microns in diameter. Both the upper and the lower limit are ill defined, varying somewhat in the different curves. The B_1 potential is well defined only in certain cutaneous and mixed nerves, certain dorsal roots and certain autonomic nerve trunks. In many other nerve trunks fibers of the type giving rise to the B_1 wave are present, but in such numbers that the potential elicited from them shows itself only as a tail to the main A wave. In visceral nerves the term B_1 is applied to the wave derived from the myelinated afferent fibers ranging from a maximum of from 10 to 12 microns to 2 microns. The range is thus wider than for the B_1 wave in cutaneous and mixed nerves. It is important to note that the fibers responsible for both the A and the B_1 potential are myelinated somatic fibers. There is no distinct gap between them in the range in size of the fibers or in physiologic properties. The absolutely refractory period as measured in vitro is from 10 to 20 per cent longer for the fibers responsible for the B_1 wave than for the fibers producing the A wave. Whether this represents a real difference in the constitution of the fibers or is the result of more rapid deterioration of the small fibers after excision or of the purely physical factors involved in stimulation is not known. The fibers for the B_2 potential are strikingly different in their physiologic properties, and the threshold is higher and the conduction rate slower than one would predict on the

basis of the ratio of the size of the fibers to the conduction rate which holds for the somatic myelinated fibers. It is apparent on the basis of experimental evidence that myelinated fibers of identical size, one somatic, the other autonomic, have quite different physiologic properties. The values for the absolutely refractory period and the chronaxia of the autonomic fiber are from four to five times those of the somatic fiber of the same size. It is somewhat confusing to apply the term B_1 and B_2 to potentials derived from fiber groups which are so different, since the B_1 group is essentially the small end of the A group. The terminology is retained to conform to that of other workers in the field.

CUTANEOUS NERVE

The conducted electroneurogram of a human cutaneous nerve shows three main potential maxima. The first of these, the A wave, has two minor crests; the second, or B_1 wave, is single, and the third, the C wave, is usually single.

When the area of potential of the nerve is plotted against the threshold, such a nerve is found to contain myelinated fibers varying from a maximum of from 15 to 20 microns (in various nerves) to 1.5 microns and a greater number of nonmyelinated than myelinated fibers. The C elevation corresponds to the nonmyelinated fibers, and the A and B crests correspond to a bimodal distribution of the myelinated fibers, the minimum between these modes falling at a diameter of about 5 or 6 microns. There are in most cutaneous nerve branches a greater number of myelinated fibers below 6 microns than above (Ranson, Droegemueller, Davenport and Fisher [5]), and the three groups of fibers increase in numerical content from the group of large to the group of small fibers. The amplitude or area of potential, however, decreases from the large to the small fibers; this is in accordance with the general finding that the amount of the potential varies approximately as the square of the diameter of the fiber—that is, as its cross-section or its mass per unit of length.

The cutaneous nerves of man differ from those of the cat and of the rabbit in that the B_1 wave is not so distinct from the A wave but is rather a low plateau following the A wave, with little or no depression between. This might be taken to indicate that the human nerves have relatively more fibers of intermediate size. However, plots of the size distribution of fibers of these nerves do not show such a difference. In the saphenous nerve of the cat and of the dog the interval between the A and the B_1 potential has been assigned to a slower conduction

5. Ranson, S. W.; Droegemueller, W. H.; Davenport, H. K., and Fisher, C.: Number, Size and Myelination of the Sensory Fibers in the Cerebrospinal Nerves, A. Research Nerv. & Ment. Dis., Proc. **15**:3, 1935.

rate in proportion to fiber diameter for B_1 fibers than for A fibers (Heinbecker, Bishop and O'Leary [6]).

This difference appears to be less striking in the human subject, and the potential picture corresponds more uniformly to the distribution of size of the fibers. However, a difference corresponding to that observed in other mammals can be shown by measurements of fiber threshold. If the plot of the area of potential versus the strength of the stimulus (chart 2) is compared with the plot of fiber area versus the reciprocal of fiber diameter or with the potential record itself as obtained after

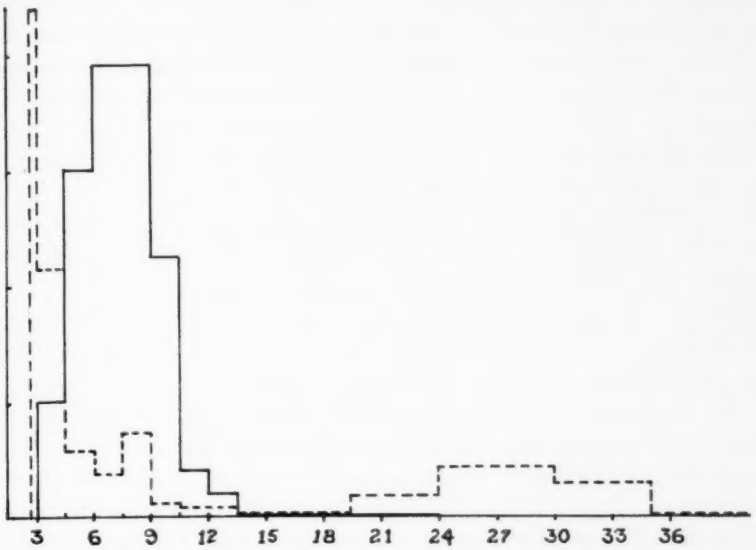

Chart 2.—Plots of increase in area of action potential against strength of stimulus for the motor nerve (solid line) plots for which are shown in chart 1 and for an adjacent sensory nerve taken from the popliteal space of the same subject (line of dashes). In this chart and in chart 4 the strength of the stimulus is measured on the x axis. The curve for action potential of the motor nerve follows the curve for fiber distribution shown in chart 1, with a single maximum, while the sensory nerve has three maxima, the first two representing overlapping elevations that comprise the A wave and the third corresponding to the B_1 wave. The rates of conduction of the fastest sensory and motor A fibers at 38 C. were 70 and 59 meters per second, respectively, and the conduction rate of the sensory B fibers was 22 meters per second, the ratio of the rate of the A fibers to that of the B fibers being 3.2 : 1. The ratio between the threshold for sensory A fibers and that for the sensory B fibers was 1 : 10. The ratio between the size of the largest fibers in the A group and that in the B group was about 3 : 1. The conduction rates of the A and B fibers of this sensory nerve are thus proportional to fiber diameter, but the thresholds of A and B fibers are not inversely proportional to diameter. In the cat, dog and rabbit the conduction rates as well as the thresholds depart from this proportionality.

6. Heinbecker, P.; Bishop, G. H., and O'Leary, J. L.: Pain and Touch Fibers in Peripheral Nerves, Arch. Neurol. & Psychiat. **29**:771 (April) 1933.

conduction, an interval appears in the first plot showing a relative lack of fibers with intermediate threshold as compared with the number of corresponding fibers of intermediate diameter. This also holds for the saphenous nerve of the cat. In the nerves of the cat, therefore, both the conduction time and the threshold of B_1 fibers are greater in relation to the diameter than the same values for A fibers. In the nerves of man only the threshold shows a pronounced discrepancy.

Between the B_1 and the C wave of a cutaneous nerve there is uniformly a wide discontinuity of potential in both the cat and man. Other striking physiologic differences are apparent when the properties of the myelinated fibers responsible for the A and B potentials are compared with the properties of the nonmyelinated fibers. The ratios between size and duration are not comparable. In the first two groups the conduction time varies approximately as the reciprocal of the diameter of the fiber, whereas in the third group this ratio does not hold, the value for the conduction time being from five to ten times as great. The values for the absolutely refractory time and the chronaxia of the fibers giving rise to the third potential maximum are from five to ten times as great as similar values for the first and second fiber groups. Similar but slight differences (from 10 to 20 per cent) exist between the physiologic properties of the fibers responsible for the first and second potentials. The values for the absolutely refractory period and the chronaxia of the second group are from 10 to 20 per cent greater than those of the first group. The fresher the preparation the less is the difference in the values for the absolutely refractory period; so it is not certain that this apparent difference in physiologic properties is real. In the living animal the two may have the same properties. Consequently, it is preferable to designate the two sets of fibers as fiber groups rather than as fiber types. Both have characteristically quick action as compared with the fibers giving rise to the third potential maximum. Average values for the threshold, conduction rate, absolutely refractory period and chronaxia for the various fiber groups are given in the table.

Functional studies have been carried out on cutaneous nerves in man (Heinbecker, Bishop and O'Leary[6]). These consisted in the stimulation of cutaneous nerves in situ, the thresholds for the different sensations and reflex effects being recorded. After excision of the nerve trunk, potential and histologic analyses were made. By correlation of the data derived from the two groups of experiments it was evident that tactile sensation is mediated by the largest myelinated fibers in the nerve and sensation for bright contact or pricking touch by smaller myelinated fibers approximately from 6 to 3 microns in diameter. The central summation of the effect of activity in the last-mentioned fibers results in pain. Studies on the order of sensory loss and its return following

the injection of procaine hydrochloride into the subarachnoid spaces have established the fact that warmth and cold are subserved by the smallest somatic myelinated fibers. The function of the nonmyelinated fibers in the cutaneous nerves of man has not been directly determined. In animals it has been shown that these fibers are derived from two sources, the dorsal roots and the outlying sympathetic ganglia, the former fibers being vasodilator, the latter vasoconstrictor. The nonmyelinated fibers of the dorsal roots also serve afferent functions. Pain definitely results from impulses in such fibers, as do reflex muscular responses (Ranson,[7] Gasser [8] and Clark, Hughes and Gasser [9]), which are characterized by their diffuseness, in contrast to the responses resulting from the excitation of the myelinated somatic fibers (Bishop and Heinbecker [10]).

Data Derived from Functional Analysis of Various Typical Nerves for Groups of Fibers Based on the Characteristic Type of Wave

A. Rates of Conduction of Waves, Expressed in Meters per Second, for Various Types of Nerves of Man

Nerve	Type of Wave			
	A	B_1	B_2	C
Saphenous	120-60	35-15	.....	1.5-0.3
Branch to gastrocnemius muscle	120-60	35-15	.....	1.5-0.3
Cervical portion of sympathetic trunk	.....	35-15	15-8	1.5-0.3
Vagus*	80	27	4.2	0.6
Phrenic*	78	...	...	0.5
Genitofemoral*	42	17	9.0	0.4

B. Values for Threshold, Absolutely Refractory Period and Chronaxia

	Types of Waves†			
	A	B_1	B_2	C
Threshold, arbitrary units	100	450	1,200	5,000
Absolutely refractory periods, σ	0.7	0.8	4-5	5-7
Chronaxia, σ	0.3	...	3	4

* Values for a particular nerve.
† Average values for all nerves.

NERVE TO MUSCLE (GASTROCNEMIUS)

The conducted action potential of a human nerve to muscle has a first elevation followed by a later potential that does not appear as a definite maximum, which is similar to the B_1 wave of the cutaneous nerve, but relatively lower. In nerves of man, as in those of the monkey,

7. Ranson, S. W.: Cutaneous Sensory Fibers and Sensory Conduction, Arch. Neurol. & Psychiat. **26**:1122 (Dec.) 1931.

8. Gasser, Herbert S.: Conduction in Nerves in Relation to Fiber Types, A. Research Nerv. & Ment. Dis., Proc. **15**:35, 1935.

9. Clark, D.; Hughes, J., and Gasser, H. S.: Afferent Function in Group of Nerve Fibers of Slowest Conduction Velocity, Am. J. Physiol. **114**:69, 1935.

10. Bishop, G. H., and Heinbecker, P.: Am. J. Physiol. **114**:179, 1935.

cat and dog, no B_2 potential is recognized. This is in keeping with the fact that there are few, if any, postganglionic myelinated autonomic fibers in nerves to muscle. In these nerves the maximum amplitude of the A potential is obtained with a strength of stimulus from two and one-half to three times the threshold value for the most irritable fibers. In many preparations very slight increase in area, except in the position of the C wave, is seen, no matter how strong the stimulus (chart 3); in other words, the B_1 potential is relatively low as compared with the A potential. In other preparations the B_1 wave is comparable

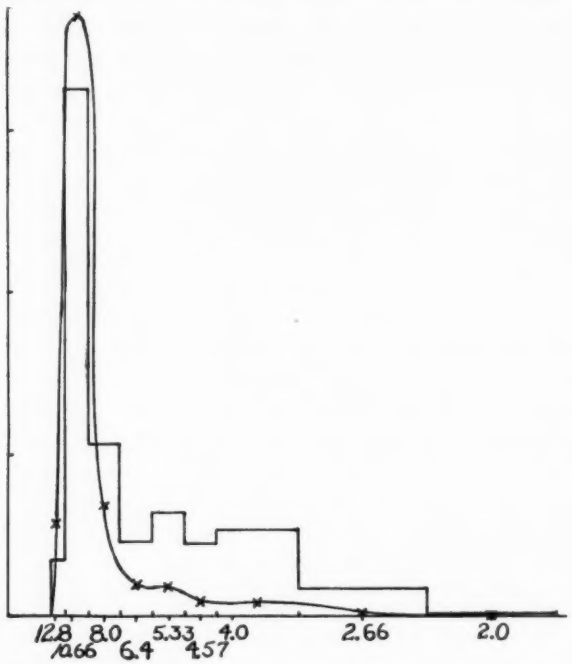

Chart 3.—Plot of the number of myelinated fibers (rectangular graph) and the area of fibers (smooth curve) against the reciprocal of fiber diameter for the motor nerve to the median head of the gastrocnemius muscle, taken at biopsy. The number of small fibers (6 microns and below) in this nerve is greater than that in the nerve plots which appear in chart 1.

to that of a cutaneous nerve (chart 4). In larger nerve trunks the range of values for the threshold which causes an increase in A potential, for fibers from the most irritable to the least irritable, is from 1 to 4 or 6, but this wider range of threshold may be assigned to the fact that in such large nerves not all fibers are equally accessible to the stimulating current. Similar relationships have been found to hold in

the cat (O'Leary, Heinbecker and Bishop [11]), in which it was also determined that the curve for height of contraction plotted against strength of stimulus had similar dimensions.

It is evident from a study of the charts for fiber size and area for motor nerves of cats after elimination of the afferent fibers that no striking increase is to be expected in the area of potential obtained on stimulating the small motor fibers, of 5 microns and less, since they amount to no more than 1 per cent of the area of the whole nerve. The variable B_1 potential following the main A elevation is, then, due chiefly to the activity of myelinated sensory fibers of the median size range rather than to the activity of the group of small motor fibers with slight effect on muscle contraction, which may innervate only muscle spindles. The C potential is less well developed in motor than in cuta-

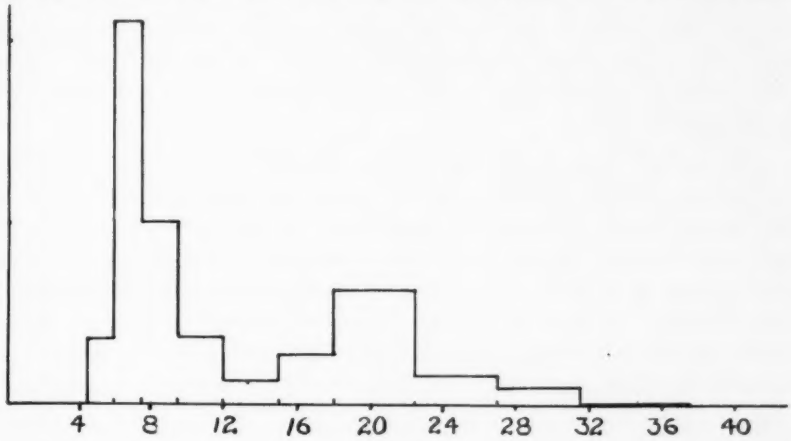

Chart 4.—Plot of increase in area of the action potential against strength of stimulus for the nerve plots for which are shown in chart 3. The bimodal character of the potential curve is much more discrete than that of the number curve. The plot for this motor nerve is thus in contrast to the plot for the corresponding motor nerve from a different subject, shown in chart 1, but it is similar to the plot for the sensory nerve shown in chart 2. This indicates that some of the fibers have a higher threshold than others in proportion to their size and are thus more readily separated when threshold is plotted on the base line than when the reciprocal of the diameter is so plotted. This occurs regularly in the sensory nerves of animals, and its occurrence in this case is taken to correspond to an unusually large component of sensory fibers in this nerve, giving rise to a typical sensory B wave, usually characteristic only of cutaneous nerves.

neous nerve trunks. This is in keeping with the fact that the nonmyelinated fibers constitute about one fourth of the total number of

11. O'Leary, J. L.; Heinbecker, P., and Bishop, G. H.: Am. J. Physiol. **110:** 636, 1935.

fibers in the nerve, whereas in the cutaneous nerve the number of nonmyelinated fibers is generally as great as or more than that of the myelinated fibers. The average values for the conduction rate, absolutely refractory period and chronaxia for the various fiber groups are given in the table.

Functional Studies of Motor Nerve to Muscle.—Direct stimulation of a human motor nerve to muscle (such as the tibial branch to the gastrocnemius muscle) yields two sensations, pressure from the larger fibers and pain from the smaller. Pain is again a summation phenomenon, a sharp pricking or stabbing sensation being experienced on stimulation just below the threshold for pain. The number of pain fibers in a motor nerve is smaller than that in a cutaneous nerve of corresponding size; so gentle manipulation of muscles is possible without pain in the conscious subject, provided that actual contact with a nerve trunk is avoided. Sensations of warmth and cold are not elicited from muscle tissue. Tonic reflexes result from activity of fibers of the group mediating pain.

More extensive functional studies have been carried out in the cat (O'Leary, Heinbecker and Bishop[11]). The close correspondence of the histologic and physiologic observations on muscle nerves of the cat and man appears to make permissible inferences as to function in man on the basis of that found in the cat. On the sensory side, the function for the different fiber groups has been established. In the cat stimulation of the nonmyelinated fibers after functional elimination of the myelinated fibers by blocking (Bishop and Heinbecker[10]) also gives rise to pain. In man pain arising from stimulation of the myelinated fibers is so overpowering that any additional effect of pain from the nonmyelinated fibers cannot be appreciated. Again, the inference that there are both myelinated and nonmyelinated pain fibers in a human nerve to muscle seems justified. Reflex vasomotor and respiratory effects are also obtained, but the separability of these fibers from sensory fibers has not been established. In man tonic reflexes result from stimulation of the myelinated fibers of the size range corresponding to that of pain fibers. In animals it has been shown that stimulation of the large afferent fibers having a size range above that of pain fibers results in release of tone if it is present in the muscle (gastrocnemius) when a muscle branch of the nerve is stimulated; otherwise no effect on tension is produced. Stimulation of fibers in size range corresponding to that of myelinated pain fibers results in contraction. The same procedures produce reverse effects in the quadriceps extensor muscle, except that if the strength and frequency are sufficient, spasmodic contractions of all the muscles in the vicinity obscure the simple coordination. Stimu-

lation of nonmyelinated fibers gives rise to vasomotor, respiratory and reflex muscular responses. The reflex muscular responses are characterized by their diffuseness.

Examination of the plots for the human nerve to muscle shows a maximum in the range of fibers of 14 microns and a second less prominent maximum for fibers of 4 microns. In all nerves fibers were distributed in all the size groups between these extremes, the form of the action potential after conduction matching the size distribution of the fibers. By degeneration experiments in the cat it has been shown that approximately 50 per cent of the myelinated fibers in a muscle nerve and 90 per cent of the nonmyelinated fibers have their cells or origin in the spinal ganglia and 10 per cent are derived from the paravertebral sympathetic ganglia. No fibers in the dorsal roots have their cells of origin within the cord (Heinbecker, O'Leary and Bishop [6]). Plots for the sensory fibers after elimination of all motor fibers by degeneration show a maximum in the large fiber range, with a progressive decrease in number corresponding to the decrease in size. Plots for nerves in which the afferent fibers have been eliminated, on the other hand, show two well defined groups even more distinctly than those for the whole nerve. The interval between the two groups falls at a diameter of from 6 to 8 microns. In the cat some evidence that the smaller group is concerned in the motor innervation of the muscle spindles has been presented, but it is not conclusive.

CERVICAL PORTION OF THE SYMPATHETIC TRUNK

In the two nerves studied, three groups of fibers were observed (chart 5): large myelinated, smaller myelinated and nonmyelinated; one nerve had so few large myelinated fibers that only a trace of a potential wave could be assigned to them. This group is variable in the cat and absent in the rabbit, and the fibers are presumably afferent. The rate of the second potential was from 10 to 7 meters per second, and the rate of the third, from 1 to 0.3 meters. The refractory period of the second, or B_2, potential was 5 sigmas, and of the C potential, 7 sigmas. The second potential was obviously the result of activity of fibers of the myelinated autonomic group, and the third, the result of activity of the nonmyelinated group.

Sections stained with osmic acid revealed three types of fibers: large and smaller thickly myelinated, small thinly myelinated and nonmyelinated fibers. Above the superior cervical ganglion a few thickly myelinated fibers of the somatic type were seen; the remainder were nonmyelinated. In man histologic studies of this portion of the sympathetic trunk and of other visceral nerves lead one to agree with the observation of Gaskell that most, if not all, postganglionic sympathetic fibers are non-

myelinated. This is similar to our observations in the rabbit, but in the cat many postganglionic fibers are also myelinated.

It has not been possible to study in the body the functions of the cervical portion of the sympathetic trunk of man. Two of us (Bishop and Heinbecker[12]) have studied these functions in detail in the cat, in which it was found that activity in the larger fibers of the preganglionic myelinated autonomic group was responsible for retraction of the nicti-

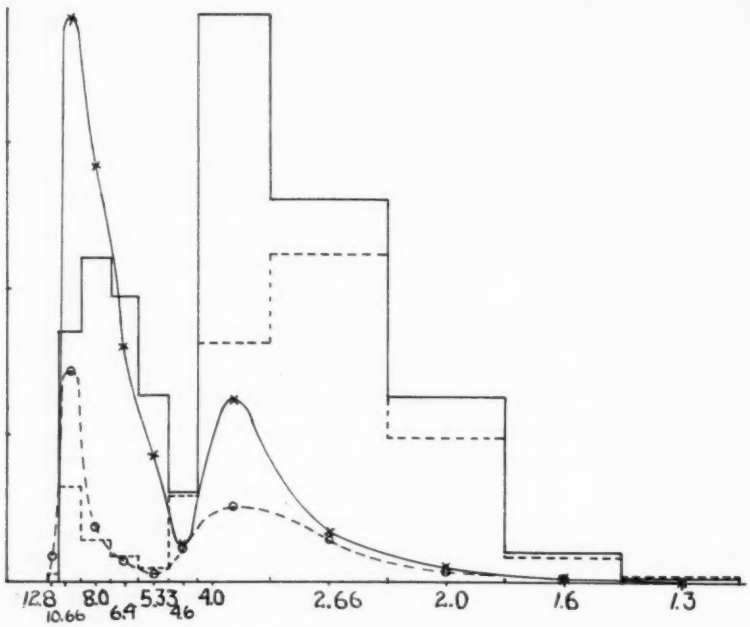

Chart 5.—Graphs for the cervical portion of the sympathetic trunk (solid line) and the abdominal portion of the sympathetic chain (line of dashes), showing the number of trunk myelinated fibers (rectangles) and the sum of the fiber areas (smooth curves) plotted against the reciprocal of the diameter. Two groups of myelinated fibers are present, the first of which is presumably sensory. This group is variable in the cervical portion of the sympathetic trunk of man and the cat, being unusually large in the nerve represented here, and is absent in the rabbit. The second group of fibers, the number but not so much the total area of which are larger, consists of autonomic motor fibers; the range of sizes for the sensory group presumably extends into the range for the motor fibers, but the group is obscured there by the latter fibers. In the rabbit few, if any, fibers are over 4 microns in diameter; in the cat when no first wave appears in the action potential, this is also true, but when a first wave precedes the wave for the autonomic component, larger fibers are present in the cross-section. It is inferred that in man no autonomic fibers are over 4 microns in diameter. Nonmyelinated fibers, which are also present, are not represented on the graph.

12. Bishop, G. H., and Heinbecker, P.: Am. J. Physiol. **100**:519, 1932.

tating membrane, dilatation of the pupil and contraction of Müller's muscle. Stimulation of the smaller preganglionic myelinated fibers resulted in constriction of blood vessels and elevation of hair. In the postganglionic fibers of man all such functions subserved by the cervical portion of the sympathetic trunk must of necessity be initiated by activity of the nonmyelinated fibers. It is probable from the studies on animals that, in general, the more quickly performed functions are likely to be controlled by activity of myelinated preganglionic fibers.

Of considerable interest has been the question of afferent fibers in the cervical portion of the sympathetic trunk. Histologic studies of the various portions of the entire cervical division of the sympathetic trunk and of the rami communicantes leave little doubt that there are present usually a few fibers definitely of the somatic type, generally varying from 12 to 3 microns (Heinbecker [13]). The number of such fibers is not great. On the basis of clinical evidence, especially the site to which pain is referred in cases of angina pectoris, it seems justifiable to conclude that certain fibers in these trunks are pain fibers. It has also been shown that nonmyelinated fibers in the sympathetic chain of the dog mediate pain. In the turtle nonmyelinated fibers in certain preparations conducted through the superior cervical ganglion in both directions without delay (Heinbecker [14]). It was considered that these fibers probably represented postganglionic fibers which synapsed in the middle or the inferior cervical ganglion. It is, however, possible that they were afferent fibers with cells of origin in certain spinal ganglia. Evidence of such fibers has not been secured in mammals. Other studies have shown that in the turtle and the cat, but not in the rabbit, depressor and other afferent fibers are present in the cervical portion of the sympathetic trunk and that some of these pass up the cervical portion of the chain, through the superior cervical ganglion, to enter the central nervous system via the ganglia of the vagus nerve. This is presumably also the condition in man.

Studies on conduction through the superior cervical ganglion of the turtle and the cat have shown that activity in the postganglionic fibers always corresponds in frequency with activity in the preganglionic fibers. There is no evidence of any independent rhythm of the postganglionic neurons as a result of their excitation by preganglionic fibers. No evidence of spontaneous activity in any outlying ganglia of the sympathetic nervous system has ever been obtained. Transmission in sympathetic motor fibers is always in one direction only—from the preganglionic to the postganglionic fibers.

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13. Heinbecker, P.: J. Thoracic Surg. **2**:517, 1933.
14. Heinbecker, Peter: Am. J. Physiol. **93**:284, 1930.

VAGUS NERVE

Functional Studies.—The conducted electroneurogram of the vagus nerve of man in the cervical region shows three potential maxima. The first is double, representing the A and B_1 waves; the second, a typical B_2 wave, and the third, a C wave. The A fibers have been shown by degeneration experiments on animals to be largely motor and sensory fibers of the recurrent laryngeal nerve, and the B_1 fibers, essentially myelinated afferent fibers of visceral nerves. The B_2 wave is derived from myelinated autonomic fibers and the C wave from nonmyelinated fibers (Heinbecker and O'Leary [15]).

The functions of the various fiber groups, both afferent and efferent, have of necessity been determined in the dog, cat and rabbit (Heinbecker and O'Leary [15]). They are briefly summarized at this point. The afferent fibers are of two types, myelinated with somatic properties and nonmyelinated with slow properties, characteristic of autonomic efferent fibers. They have reflex vasomotor and respiratory effects and sensory effects. The vasomotor fibers include both pressor and depressor types. In the myelinated group in the rabbit the larger vasomotor afferent fibers, from 14 to 8 microns in diameter, of lowest threshold are purely depressor, and the somewhat smaller fibers, of the size range corresponding to that of the fibers of the depressor nerve, are mostly pressor (Bishop, Heinbecker and O'Leary [16]). In man no separate depressor fibers have been found in the cervical region which was studied, and consequently the vagus nerve contains most, if not all, the fibers of this type. Separate depressor branches are described just distal to the nodose ganglion in man. In the rabbit, by alterations in the strength and frequency of the stimulus, either a decrease or an increase in blood pressure can be secured on stimulation of the vagus nerve. The effect of frequency of stimulation of the vagus nerve in giving a decrease in pressure on slow stimulation and an increase on fast stimulation may be assigned to the stimulation of both pressor and depressor afferent fibers in each case, with different orders of temporal summation at the centers, so that the effect of increasing the frequency of pressor stimulation is greater than that of increasing the frequency of depressor stimulation. Similar, if not identical, conditions are presumed to hold in man.

The afferent fibers concerned with respiration likewise appear to be of two types, those causing acceleration and those causing inhibition or slowing of respiration. In practically all rabbits an increase in strength and frequency reverses an initial acceleration of respiration to marked slowing. We have found it impossible to stop the respiration by stimu-

15. Heinbecker, P., and O'Leary, J. L.: Am. J. Physiol. **106**:623, 1933.

16. Bishop, G. H.; Heinbecker, P., and O'Leary, J. L.: Am. J. Physiol. **109**: 409, 1934.

lation of the vagus nerve on one side in lightly anesthetized rabbits. It is easy to stop the respiration if the depth of anesthesia is increased. With the degree of anesthesia which does not depress blood pressure, the results of increasing the stimuli are, first, increase in frequency and decrease in depth of respiration, then reversal of these effects until the respiration may appear almost normal, except that less pause occurs between expiration and inspiration, and, finally, greater slowing and depth until gasping results. After strong stimulation struggling may result, but whether this is due to potentially painful stimuli we have not ascertained. The latency of struggling is certainly much greater than after stimulation of the saphenous nerve, for instance. Our

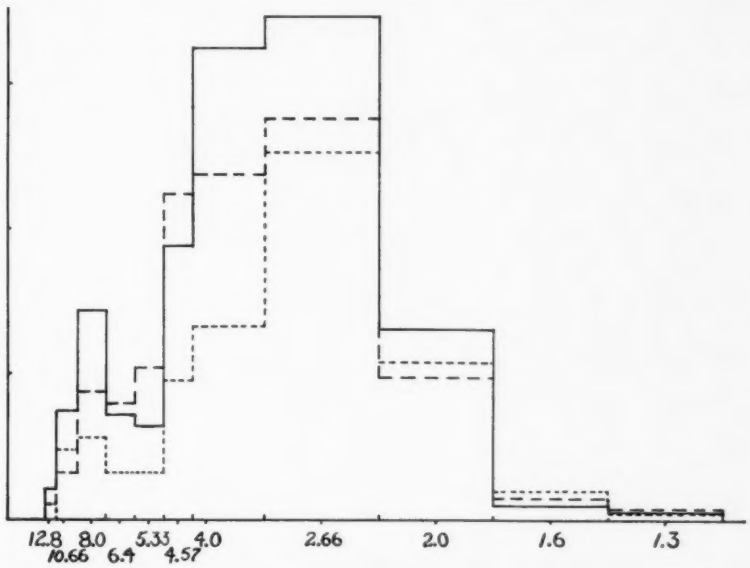

Chart 6.—Graphs for the cervical portion of the vagus nerve, three fascicles of which were counted separately, showing the number of myelinated fibers plotted against the reciprocal of the diameter.

results indicate that two groups of fibers are involved in respiratory as in circulatory reflexes, the acceleratory fibers lying toward the larger fiber range, the inhibitory fibers toward the small fiber range.

The question of the presence of pain fibers in the vagus nerve has been disputed. In cats, on stimulation of the main vagus trunk below the level of the recurrent laryngeal nerve, we have elicited the various reflex phenomena associated with pain. The accommodation to such stimuli is rapid. It is thought that the vagus nerve probably contains pain fibers but that their number is limited. It is probable that the vagus nerve in man and animals contains afferent fibers concerned with

the sensations of thirst, hunger and nausea. If the recurrent laryngeal nerve is similar to other nerves to muscle, it contains pressure and pain fibers.

The motor functions of the vagus nerve have been investigated in the rabbit and cat. The largest myelinated fibers are motor and supply skeletal muscle. Small myelinated autonomic fibers have been shown to be the principal inotropic and chronotropic depressor fibers to the heart. The nonmyelinated fibers cause constriction of the bronchial tubes and inhibition or excitation of peristaltic movements in the upper

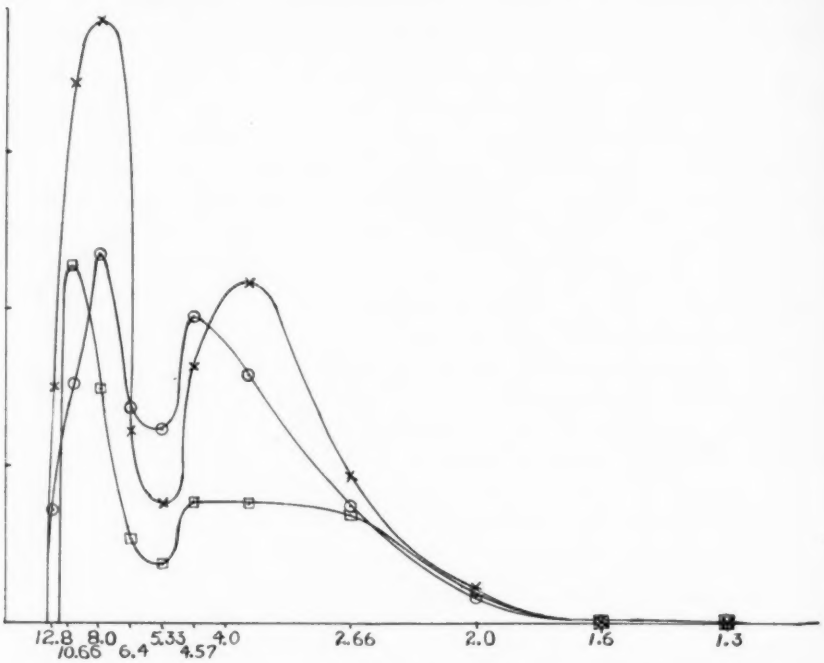

Chart 7.—The nerve was employed for which plots appear in chart 6, but total areas of fiber groups are plotted against reciprocals of diameter. As in the case of the sympathetic nerve, the first elevation represents only somatic fibers (motor and sensory), while the second group includes the autonomic fibers. That the second size group also includes somatic sensory fibers can be demonstrated in animals, in which the stimulation of these fibers results in vascular and respiratory reflexes and pain. The group of nonmyelinated fibers of the vagus nerve of animals contains an autonomic and an afferent component. The number of nonmyelinated fibers (not represented on the graph) is greater than the total number of myelinated fibers, and a large C wave is present.

portion of the bowel. It is believed that there are in this case also two sets of fibers, excitatory and inhibitory. Peripheral stimulation of the nonmyelinated fibers gives rise to reflex struggling and to changes in

respiration. The mechanism involved has not been determined. It is possible that peripheral effects are produced which cause the excitation of sense organs within the structures involved. The afferent fibers which are stimulated must enter the central nervous system by the sympathetic nerves and the dorsal roots, for the effect of stimulation is still obtained after section of both vagus nerves. A fuller study of this phenomenon is in progress.

Histologic Studies.—The cervical portion of the vagus trunk in man is divided into fascicles. In the monkey, dog, cat and rabbit no such

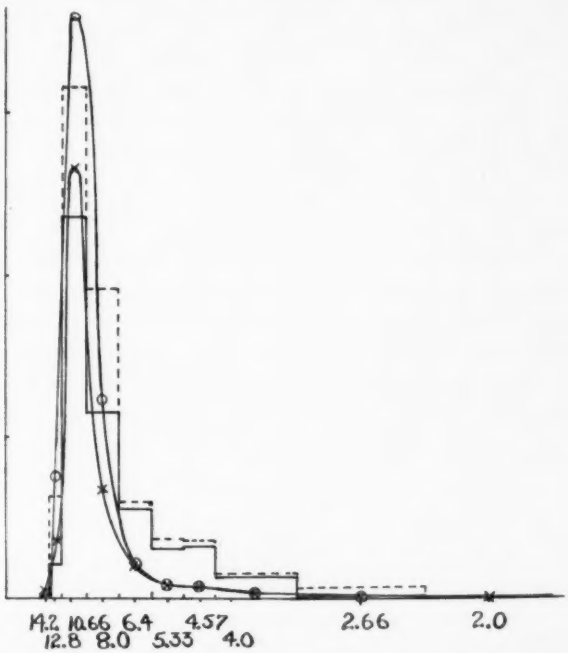

Chart 8.—Graphs for the phrenic nerve, two fascicles of which were counted, showing the number (rectangular curves) and total areas of fibers (smooth curves) plotted against the reciprocals of diameter. The typical unimodal curve extends into a tail, with no B elevation, which is also characteristic of the plot of action potentials for this nerve. Some of the smaller fibers, corresponding to the group of fibers 6 microns and less in diameter in muscle and cutaneous nerves, convey pain in animals and presumably convey pain in man, but their number is too small to show in either the plots of area or the records of action potential.

divisions exist, but it is possible to recognize in these animals a region of fibers which in large measure compose the recurrent laryngeal nerve. The composition of the individual fascicles varies, that of the recurrent laryngeal nerve having a great number of large thickly myelinated fibers. Certain of the other divisions are, for the most part, nonmyelinated

and presumably, therefore, are distributed ultimately to the abdominal viscera. The composition of others is fairly well mixed, there being certain large and thickly myelinated fibers, smaller and more thinly myelinated fibers and nonmyelinated fibers. The fiber plot of several of these fascicles is shown in chart 6. There are two maxima for the myelinated group; a third maximum would appear if the nonmyelinated fibers were represented in the plot.

PHRENIC NERVE

The conducted electroneurogram of the phrenic nerve of man shows two potential maxima. The first has a tail, such as is seen for typical nerves to muscle. The second is very low and has the characteristics

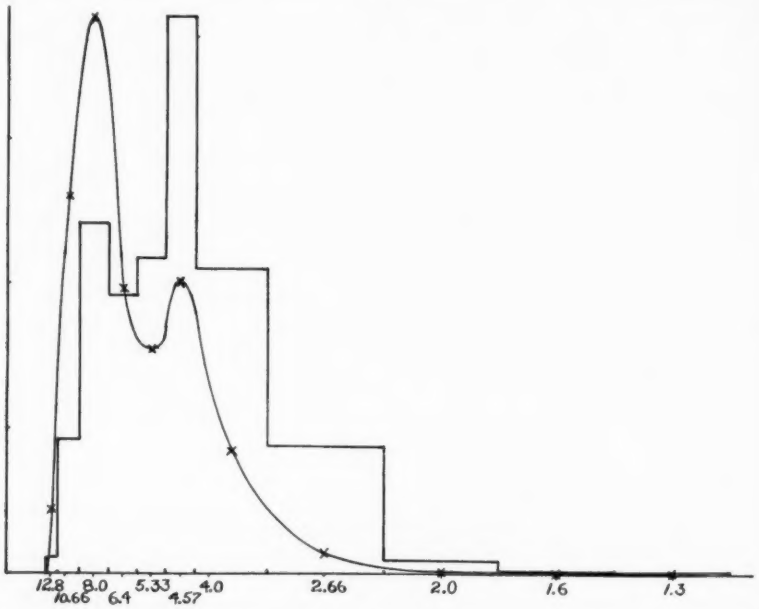

Chart 9.—Graph for the median branch of the genitofemoral nerve, showing the number of fibers (rectangular curve) and the areas (smooth curve) plotted against the reciprocal of fiber size. The second maximum can presumably be assigned in part to autonomic fibers, although small sensory fibers are present in animal nerves. The first peak represents somatic afferent fibers. In man a first elevation of potential corresponds to this first fiber group. Following this is a double elevation, corresponding to the second group, the first part of which presumably represents the somatic component of small fibers and the second part, the autonomic component, which can be separated on the basis of threshold and conduction rate but not on the basis of size distribution.

of the C wave. The values for the conduction rate, refractory period and chronaxia are presented in the table.

The plots for the fibers are similar in character to plots for typical nerve trunks to muscle (chart 8).

We have determined the function of the fibers in the phrenic nerve of the cat. The largest fibers are motor. Afferent fibers, some of which are pain fibers, are present. They have muscular reflex, respiratory and vasomotor effects. The nonmyelinated fibers are derived partly from the spinal ganglia and partly from the paravertebral sympathetic ganglia. Their function is presumably that of nonmyelinated fibers of nerves to muscle in general, i. e., afferent and vasomotor efferent.

GENITOFEMORAL NERVE (MEDIAL DIVISION)

The conducted electroneurogram of the genitofemoral nerve of man shows three potential maxima. The first of these is complex and has the characteristics of potentials derived from somatic nerve fibers. The second has a high threshold, a slow conduction rate and a refractory period such as is found in potentials derived from myelinated autonomic fibers. In this nerve these fibers probably innervate the dartos muscle, as in no other nerve to striated muscle has a potential with such characteristics been observed. The third potential is a typical C wave, derived from the nonmyelinated fibers. The quantitative data for this nerve are given in the table, and the plot for the fibers is shown in chart 9.

This nerve has also been studied in the cat and the rabbit, in which the B_2 potential characteristic of autonomic fibers is much less prominent, if present at all. The larger fibers are without motor effects, but, contrary to the usual situation in muscle nerves, in which the larger fibers account for practically all the tension, the cremasteric muscle is innervated by smaller fibers in the somatic B_1 range.

COMMENT

The chief motivation of this investigation of human nerves has been to determine to what extent the data derived from the study of the more easily available animal material is applicable to the human subject. The expectation has been confirmed that such results are generally applicable, this expectation being based on the finding of close similarities between the nerves of the various laboratory animals. Too extreme generalizations are not justified, but while minor differences exist, it is proper to state that in any given respect a human nerve is practically identical in its general composition and function with the corresponding nerve of some animal. An illustration of the meaning of this distinction may be drawn from the cervical portion of the sympathetic trunk.

In the rabbit the postganglionic fibers are practically all nonmyelinated, with corresponding properties. In the cat a group of preganglionic fibers of low threshold (larger size) synapse with postganglionic

myelinated fibers, while a group of preganglionic fibers of high threshold synapse with nonmyelinated fibers, as in the rabbit. In this respect, the monkey Macacus rhesus is similar to the cat, and man, to the rabbit. Aside from the differences associated with myelination, all these nerves correspond, one group of fibers with another, and presumably also in their functional relations in the body, and the properties of the myelinated or the nonmyelinated fibers, respectively, are practically identical in the different nerves of the various animals studied. Aside from such differences, which involve details in which the common laboratory animals differ from each other as much as they do from man, there may be minor differences in the distribution of fibers into specific trunks destined for a given region of the periphery. The second difference between human nerves and the nerves of other animals, mentioned previously, that is, the presence in some human nerves to muscle of a B_1 elevation of a type about as distinctive as that of cutaneous nerves, which we have not observed in the nerves of animals, may be taken to indicate a richer supply of sensory fibers to the muscle in man than in the cat. But since this plenitude of B_1 fibers is not always exhibited by a given nerve (the branch to the median head of the gastrocnemius muscle has been examined in numerous cases), this finding more probably means that sensory fibers passing to other regions than that which the motor fibers immediately innervate are contained in this branch. It is possible that the various fascicles innervating the median head of the gastrocnemius vary in the relative number of motor and sensory fibers which they carry.

Further than this, it was hoped that analysis of typical normal human nerves might be of value for comparison in cases of pathologic conditions involving peripheral nerves. The diagnosis of such conditions is complicated by two sets of circumstances, first, a certain degree of variability in specific nerves, as already discussed, and second, the dependence of normal function of the excised nerve on its treatment at operation and on the length of time before examinaiton. The small fibers of most nerves are depressed after removal from the body sooner than the large, and the large fibers are more susceptible than the small to injury by stretching or compression. It is therefore considered that any nerve so utilized for diagnosis must be examined both histologically for distribution of fibers, physiologically for distribution of potential and, if possible, functionally by stimulation in the body before excision; and its contribution to a pathologic condition should then be interpreted only in the light of the care with which it was handled, possible contact with anesthetic, etc., as well as in connection with the other pathologic aspects in the case.

SUMMARY

Human nerves have been examined from material taken at autopsies which were performed promptly and at surgical operations in which procedures were used identical with those employed in the analysis of the nerves of laboratory animals. These procedures involve recording the action potentials in a moist chamber at body temperature promptly after excision, histologic examination of the nerves with the osmic acid and pyridine-silver methods of fixation and staining, including counting the fibers into groups on the basis of size, and, when possible, functional examination of the responses to stimulation of the nerves in the body before excision and of sensory and motor responses of the region of the body innervated before operation.

Analyses of the following typical nerves are presented: nerves to the skin, the nerve to the median head of the gastrocnemius muscle, the cervical portion of the sympathetic trunk, the vagus nerve, the phrenic nerve and the medial division of the genitofemoral nerve. Their function in the body in relation to their fiber content is discussed on the basis of some experiments on man and extensive examination of the corresponding nerves in animals.

The physiologic properties of human nerve fibers, of corresponding size and type, are practically identical with those of the ordinary laboratory animals, such as the monkey, cat, dog and rabbit. Certain differences exist between the various animals, including man, as to which type of fiber (for instance, the myelinated or the nonmyelinated postganglionic fibers in the cervical portion of the sympathetic trunk) is utilized to subserve a given function in the body. A certain degree of variation also exists in the distribution of fibers into the various branches of a nerve trunk innervating a given region.

Owing to these complications and to the further possibility that the treatment of a nerve at operation without proper precautions is liable to affect its function on subsequent examination, the investigation of nerves as a means of diagnosis should include histologic, physiologic and functional studies, and the results should be interpreted in the light of the circumstances, pathologic and manipulatory, under which the material was obtained.

RELATIONSHIP OF THE SYSTOLIC TO THE DIASTOLIC BLOOD PRESSURE IN SCHIZOPHRENIA

THE EFFECT OF ENVIRONMENTAL TEMPERATURE

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The relationship of the systolic to the diastolic blood pressure has been studied by Hoskins and Jellinek.[1] They reported for large groups of normal and schizophrenic subjects between-individual correlation coefficients of 0.43 ± 0.05 and 0.62 ± 0.05, respectively. The corresponding regression coefficients were 0.377 and 0.521. The more constant relationship of these variables for the patients has been interpreted as indicating a tendency of the cardiovascular system to approach more closely than normal a rigid hydrodynamic system.

The autonomic nervous system is intimately concerned with cardiovascular regulation. A pharmacodynamic investigation of that system has shown the effect of certain drugs on the relationship of the systolic to the diastolic blood pressure. Freeman and Carmichael[2] injected epinephrine, the sympathomimetic drug, intravenously. This caused the correlation coefficient in patients to drop from 0.52 to 0.18. If an injection of epinephrine caused the lowering of the correlation coefficient to such an extent, it seems that stimulation of the sympathetic system would similarly disrupt this relationship of the systolic to the diastolic blood pressure. Ergotamine, a drug which paralyzes the motor fibers of the sympathetic system, was then similarly employed.[3] The correlation coefficient in patients increased from 0.44 to 0.77.

It therefore appears that a high correlation coefficient possibly indicates a lack of function of the sympathetic system, while a low correlation coefficient indicates the reverse. Since it has been found that a

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From the Research Service of the Worcester State Hospital and the Memorial Foundation for Neuro-Endocrine Research.

1. Hoskins, R. G., and Jellinek, E. M.: The Schizophrenic Personality with Special Regard to Psychologic and Organic Concomitants, A. Research Nerv. & Ment. Dis., Proc. **14**:211, 1933.

2. Freeman, H., and Carmichael, H. T.: A Pharmacodynamic Investigation of the Autonomic Nervous System in Schizophrenia: I. Effect of Intravenous Injections of Epinephrine on the Blood Pressure and Pulse Rate, Arch. Neurol. & Psychiat. **33**:342 (Feb.) 1935.

3. Freeman, H., and Carmichael, H. T.: Unpublished data.

group of schizophrenic patients has a higher correlation coefficient, that is, a more rigid relationship of the systolic to the diastolic blood pressure than a group of normal subjects it has been postulated that the vasomotor responses to changing conditions are relatively sluggish in the schizophrenic patient. If this postulate is correct, the schizophrenic patient would be characterized by "sluggish sympathetic reactivity." [1]

The interpretation of the cardiovascular system as approaching more closely than normal a rigid hydrodynamic system lends itself to an anatomic as well as to a physiologic explanation. Lewis,[4] in his discussion of the circulatory system in schizophrenic patients, referred to a greater than normal elasticity of the arterial vessels. If his findings are characteristic, then under similar physiologic stresses the correlation coefficients of the patients would be expected to be lower than those of the normal controls. Since the reverse is true, an anatomic basis does not seem to explain satisfactorily the experimental findings. Furthermore, Fulstow [5] reported that a normal and not an aplastic circulatory system was characteristic in schizophrenic subjects.

The purpose of this report is not only to present confirmatory data for the preceding observations but to show the effect of an increase in the environmental temperature on the relationship of the systolic to the diastolic blood pressure. In a previous report [6] the differential effect of warm air on the rectal and oral temperatures of schizophrenic and normal subjects was discussed. It was shown that under the stimulation of an increase in the environmental temperature under nonbasal conditions the patients' mean oral and rectal temperatures increased about twice as rapidly as did those of the normal subjects. If this lowered resistance to heat can be assumed to be dependent on intrinsic factors, an inadequate vasomotor response would seem to be present. The data to be presented will aid in the elucidation of the mechanisms involved.

METHOD

The experimental procedure, which has been described in detail,[6] is here given briefly. Twenty-six schizophrenic patients and sixteen normal men came in pairs to the experimental room on two separate occasions. All the experiments began about one hour after the noon meal. On both days the subjects lay quietly, completely unclothed, for three and a half hours for observation. After the first half-

4. Lewis, N. D. C.: The Constitutional Factors in Dementia Praecox, Nervous and Mental Disease Monograph 35, Washington, D. C., Nervous and Mental Disease Publishing Company, 1923.

5. Fulstow, M.: Observations on the Weight of the Heart in Schizophrenia and Other Mental Disorders, A. Research Nerv. & Ment. Dis., Proc. **5**:310, 1928.

6. Gottlieb, J. S., and Linder, F. E.: Body Temperatures of Persons with Schizophrenia and of Normal Subjects: Effect of Changes in Environmental Temperature, Arch. Neurol. & Psychiat. **33**:775 (April) 1935.

hour and at every half-hour thereafter (a total of seven periods), the following readings were taken: room temperature, relative humidity of the room, rectal and oral temperatures, systolic and diastolic blood pressures and pulse rate. The blood pressures were measured by the auscultatory method with a mercury type of sphygmomanometer. The diastolic pressure was recorded at the change from the loud to the soft (fourth to fifth) sound. The radial pulse rate was counted for a full minute.

The experimental chamber was a cylindric, brick-lined, windowless room measuring 13 ft. (3.96 meters) in diameter by 8 ft. (2.43 meters) in height. The room temperature was controlled by the regulation of eight electric heaters. The supply of fresh air was adequate, and air currents were reduced so that they were imperceptible to nude subjects. Relative humidity was measured by means of a sling psychrometer.

On the first day, called the "constant heat day," the room temperature was maintained between 23.1 C. (73.6 F.) and 23.9 C. (75 F.) for the entire three and a half hours. The mean relative humidity varied from 44.5 to 42.3 per cent. On the second day, called the "varied heat day," after the first series of readings

TABLE 1.—*Between-Individual Correlation and Regression Coefficients of Systolic and Diastolic Blood Pressures*

	Constant Heat Day		Varied Heat Day	
	Correlation Coefficient	Regression Coefficient	Correlation Coefficient	Regression Coefficient
16 Controls				
First period	0.30	0.15	0.36	0.17
Seventh period	0.55	0.33	0.64	0.43
26 Patients				
First period	0.64	0.60	0.74	0.86
Seventh period	0.59	0.37	0.84	0.64

the room temperature was raised rapidly from 23 C. (73.4 F.) to 33.6 C. (92.5 F.). The mean relative humidity dropped from 43.1 to 30.9 per cent. The changes in the relative humidity were dependent on the changes in the room temperature.

RESULTS AND COMMENT

In table 1 are given the between-individual correlation and regression coefficients for both normal and schizophrenic subjects at the beginning and at the end of both the constant and the varied heat day. For every comparable period the coefficients are higher for the patients than for the normal subjects. In ordinary circumstances no significance would be attached to differences or changes in correlation coefficients arising from such small samples. Since these results, however, are in line with those obtained for representative large samples,[1] they become significant by the criterion of consistency. This consistency attaches more to the trends than to the actual face values of the figures. Examination of the coefficients during the first period of the constant heat day shows the correlation coefficient to be 0.64 for the patients and 0.30 for the normal controls. Likewise the regression coefficients are 0.60 and 0.15, respectively.

The heterogeneous stimuli which existed pre-experimentally, such as the mild exercise in walking to the experimental room, talking and the act of disrobing, appeared to affect the normal and schizophrenic groups differently. If one conceives of the blood vessels as being either fixed in diameter or able to change similarly for all the members of the group in response to vasomotor impulses, the relationship between the systolic and the diastolic blood pressure would be expected to be close. It therefore seems that the blood vessels of the patients, in spite of various stimuli, were relatively similar in responsiveness for the entire group. For the normal subjects, however, the tonus of the blood vessels in response to the various sympathetic impulses differed considerably from one subject to another as indicated by relatively different degrees of vasoconstriction or vasodilatation.

The coefficients for the last reading on the constant heat day indicate the effect of relatively constant stimuli on the patients and controls. The normal subjects showed an increase in both the correlation and the regression coefficient. The correlation coefficient increased from 0.30 during the first period to 0.55 during the last period, and the regression coefficient increased from 0.15 to 0.33. The corresponding correlation coefficient for the patients decreased. The regression coefficient decreased from 0.60 to 0.37. Thus the trends for the patients and normal subjects went in opposite directions, yet approached each other and became fairly similar.

It seems, then, that under uniform conditions which demand a minimum of vasomotor impulses to maintain the "steady state," the functioning of the peripheral blood vessels of the normal subjects approached that of the patients. Furthermore, with the decrease in heterogeneous stimuli, it appears that the sympathetic system decreased in function in the normal group even to the extent of approaching that found in the schizophrenic group under various conditions.

From table 1 it is evident that the relationship of the systolic to the diastolic blood pressure was fairly similar during the first period of the varied heat day to the corresponding period on the constant heat day for both the normal and the schizophrenic group. Since the experimental conditions were the same on the two days during the first period, the consistency of these findings points to the general reliability of the results.

However, during the seventh period of the varied heat day the correlation coefficient increased to 0.64 and the regression coefficient to 0.43 for the normal subjects. These increases were slightly more than those for the corresponding period on the constant heat day. For the patients the reading on the varied heat day during the seventh period showed a correlation coefficient of 0.84 and a regression coef-

ficient of 0.64. These coefficients are distinctly larger than the corresponding ones on the constant heat day. The manifestations of the physiologic changes occurring as a result of the stimulation of warm air suggest parasympathetic activity. The increase in these coefficients can be ascribed to an almost complete inactivity of the sympathetic nervous system.

In order to obtain additional information, within-individual correlation and regression coefficients of systolic to diastolic blood pressure were obtained by an analysis of covariance.[7] This is an estimate of the average correlation obtaining within the individual. The results are given in table 2.

The within-individual correlation coefficients for the normal subjects are low—0.29 on the constant heat day and 0.32 on the varied heat day. The correlation coefficients for the patients are consistently higher—0.45 on the constant heat day and 0.55 on the varied heat day.

TABLE 2.—*Within-Individual Correlation and Regression Coefficients of Systolic and Diastolic Blood Pressures* *

	Within-Individual	
	Correlation Coefficient	Regression Coefficient
16 Controls		
Constant heat day	0.29	0.36
Varied heat day	0.32	0.29
26 Patients		
Constant heat day	0.45	0.43
Varied heat day	0.55	0.65

* The coefficients were obtained by analysis of covariance.

Similarly, the within-individual regression coefficients are larger for the patients than for the normal controls. Jellinek,[8] who has obtained within-individual and separate correlation coefficients from a large group of data for fifty-two schizophrenic patients, found a mean of 0.59, with the distribution skewed to the higher values. It seems, therefore, that among the patients not only is there a more constant systolic-diastolic blood pressure relationship from one to another than in normal subjects but this relationship is closer for the individual patient also.

The higher values obtained for the patients in both the within-individual and the between-individual correlation and regression coefficients seem indicative of stability of the vascular bed. As the level of the blood pressure changes, the systolic and diastolic blood pressures retain a constant relationship. This implies one of two possi-

7. Snedecor, G. W.: Calculation and Interpretation of Analysis of Variance and Covariance, Ames, Iowa, Collegiate Press, 1934.

8. Jellinek, E. M.: Unpublished data.

bilities: Either the vascular bed has lost its elasticity of function and the caliber of the vessels changes with difficulty; or, if vascular changes occur, they occur uniformly throughout the organism.

Under the stimulation of heat there is an inhibition of sympathetic vasomotor impulses. This is reflected in the large increase of the correlation and regression coefficients for the normal subjects. The coefficients for the patients showed only slight insignificant changes under direct heat stimulation. Their original level was so high that there was less chance of their becoming much greater. This seems to indicate that for the patients there is a lack or inhibition of sympathetic vasomotor impulses even at the beginning of the experiment.

Under heat stimulation and nonbasal conditions the oral and rectal temperatures of the patients increased about twice as rapidly as did those of the normal subjects. This inadequate dissipation of heat seems to occur in the patients because of the static nature of the vascular bed, caused possibly by an abnormal unresponsiveness of the sympathetic nervous system.

SUMMARY

A method is described whereby the within-individual and between-individual correlation and regression coefficients of the systolic and diastolic blood pressures of twenty-six schizophrenic patients and sixteen normal subjects were compared when both groups were under the influence of an increase in the environmental temperature. It was found that:

1. The patients consistently had higher correlation and regression coefficients at the first and last periods on both the constant heat and the varied heat day.

2. Under the experimental conditions the between-individual coefficients increased for the normal subjects from the first to the last values. The corresponding coefficients for the patients did not change significantly.

3. The within-individual correlation and regression coefficients were consistently higher for the patients than for the normal subjects.

CONCLUSION

This study indicates that the schizophrenic patient possesses a relatively static vascular bed due presumably to an abnormal unresponsiveness of the sympathetic nervous system.

DISSEMINATED SPINAL ARACHNOIDITIS

ITS DIAGNOSIS AND TREATMENT WITH ROENTGEN RAYS

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Sir Victor Horsley [1] attributed to Spiller [2] priority in the recognition of spinal arachnoiditis as a clinical entity. Earlier references to adventitious proliferations of the arachnoid had been noted by Hewett [3] in 1845 and Coote [4] in 1850. Later, contributions were made by Oppenheim [5] and Krause,[6] and more recently the excellent study by Stookey [7] was published. Stookey's contribution served to throw valuable additional light on the diagnostic and surgical aspects of this condition. During the past five years there have been reports by various European observers: Faure,[8] Brouwer,[9] Schaeffer,[10] Barré,[11] Metzger,[12] Cairns [13]

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1. Horsley, Victor: A Clinical Lecture on Chronic Spinal Meningitis: Its Differential Diagnosis and Surgical Treatment, Brit. M. J. **1**:513, 1909.

2. Spiller, William: A Case of Intradural Spinal Cyst with Operation and Recovery, Univ. Pennsylvania M. Bull. **16**:27, 1903.

3. Hewett, Prescott: On Extravasation of Blood into the Cavity of the Arachnoid, and on the Formation of the False Membrane Which Sometimes Envelops These Extravasations, Med.-Chir. Tr. **28**:45, 1845.

4. Coote, H.: On the Formation of Adventitious Membranes in the Sack of the Arachnoid, M. Times **1**:306, 1850.

5. Oppenheim, H.: Beiträge zur Diagnostic und Therapie der Geschwülste im Bereich des centralen Nervensystems, Berlin, S. Karger, 1907, p. 146.

6. Krause, F.: Zur Kenntnis der Rückenmarkslähmungen, Verhandl. d. deutsch. Gesellsch. f. Chir. **36**:598, 1907; Zur Kenntnis der Meningitis serosa spinalis, Berl. klin. Wchnschr. **43**:827, 1906.

7. Stookey, Byron: Adhesive Spinal Arachnoiditis Simulating Spinal Cord Tumor, Arch. Neurol. & Psychiat. **17**:151 (Feb.) 1927.

8. Faure-Beaulieu, M., and Goldberg, R.: Récidive d'une arachnoïdite spinale cliniquement guérie depuis six mois, Rev. neurol. **2**:88, 1930.

9. Brouwer, B.: Ueber Arachnoiditis adhaesiva circumscripta, Deutsche Ztschr. f. Nervenh. **117**:38, 1931.

10. Schaeffer, H., and de Martel, T.: Arachnoïdite spinale circonscrite: intervention opératoire; guérison, Rev. neurol. **1**:413, 1930.

11. Barré, J. A.: (*a*) Arachnoïdite et sclérose en plaques, Paris méd. **2**:297, 1929; (*b*) Etude sur l'arachnoïdite spinale et l'arachnoïdite de la fosse cérébrale postérieure, Rev. neurol. **1**:879, 1933.

12. Metzger, O. C.: Essai sur l'arachnoïdite spinale d'après dix cas personnels, Paris, Gaston Doin & Cie, 1932.

13. Cairns, H., and others: Discussion on the Surgery of the Spinal Cord, Proc. Roy. Soc. Med. (Sect. Surg.) **23**:1, 1930.

and others, and the condition has been referred to as circumscribed spinal arachnoiditis, meningitis circumscripta or serosa and adhesive spinal arachnoiditis. In the foregoing communications emphasis had been placed almost exclusively on the type of arachnoiditis that clinically simulates tumor of the spinal cord. The purpose of this paper is to call attention to the type which presents a somewhat different picture and is here termed disseminated spinal arachnoiditis.

By the term disseminated spinal arachnoiditis is designated a non-suppurative inflammatory process of the arachnoid membrane investing the spinal cord and roots, with lesions at various levels. The dissemination of the lesions in the spinal arachnoid membrane produces a syndrome of multiple involvement of the roots; occasionally slight manifestations of implication of the spinal cord develop subsequent to the evidence of radicular irritation. The symptomatology is predominantly that of involvement of the posterior roots. Invariably the disease tends to assume a subacute or chronic course.

CLINICAL FEATURES

The history of the symptoms invariably extends over several months before the patient comes under observation in the hospital. The onset is gradual and without fever. A most striking feature of the syndrome is the severe pain, which resembles radicular pain and yet is so peculiar that Horsley called attention specifically to its nature. Not as sharply circumscribed as the radicular pain commonly associated with tumor of the spinal cord, it resembles the burning sensation sometimes experienced by a tabetic patient in the extremities or over the trunk. The pain is not confined to one zone throughout the course of the disease, for there is a tendency for this sensation to be felt first in one or more extremities and weeks or months later in a distant part. The objective neurologic findings consist of sensory disturbances which assume a radicular pattern, alteration of the deep reflexes and, as suggestive evidence of disease of the cord, some abnormality in the skin or plantar reflexes. There has been no history of impairment of the sphincters in this condition; Barré [11b] also was impressed with this point. In one instance in the present series, in a diabetic patient, there was evidence of polyneuritis in addition to disseminated spinal arachnoiditis. In two cases there were fibrillation and atrophy of the muscles of the thigh.

It is conceivable that spinal arachnoiditis may occur in association with inflammatory disease of bones, i. e., arthritis, and the patients in this series showed evidence of such disease roentgenographically in several instances.

The symptom complex which this condition evokes recalls the clinical picture described by Oppenheim and Erb [14] as chronic syphilitic meningitis. In none of my cases was there any serologic evidence of syphilis.

DIAGNOSIS

The diagnosis of this condition is based on two principal criteria: the history and clinical findings of a polyradicular syndrome and evidence of some obstruction in the spinal subarachnoid space. Such evidence consists of demonstration of partial or total block by the Queckenstedt test [7] or by iodolography,[15] or myelography. The latter method is strikingly graphic in visualizing the disseminated lesions, occasionally even when the Queckenstedt test reveals no abnormality. The reverse of this phenomenon, viz., indication of block by the Queckenstedt test, with no demonstrable arrest of the iodized oil, has also been observed.

Myelography, or the intrathecal injection of a contrast substance, is of great value when the clinical picture vaguely suggests the presence of a transverse lesion of the spinal cord and when there is a history of pain in a remote area which is difficult to reconcile with a single compressing lesion. Stookey stated that if the extensive character of the pathologic process could be demonstrated, operative intervention often would be precluded. Such information can be obtained by the judicious employment of iodized oil; but it must be added that surgical intervention is usually necessary if there is moderate or marked compression of the spinal cord.

ETIOLOGY

The pathogenesis of arachnoiditis subsequent to purulent meningitis or proved syphilitic meningitis is obvious. A case of spinal arachnoiditis which developed after purulent meningitis was reported by me in 1934.[16]

Trauma to the back has been held by some observers (Barré, Metzger) to be the causative factor in certain cases. Arachnoiditis has been observed occasionally in a case of multiple sclerosis.[11a] Horsley expressed the belief that venereal infection plays an important rôle; Oesterreicher [17] also was impressed with a syphilitic etiology. In the

14. Erb, W. H.: Chronic Syphilitic Meningitis, in Oppenheim, H.: Diseases of the Nervous System, ed. 5, Philadelphia, J. B. Lippincott Company, 1908, vol. 1, p. 307.

15. Globus, J. H., and Strauss, I.: Intraspinal Iodolography: Subarachnoid Injection of Iodized Oil as an Aid in the Detection and Localization of Lesions Compressing the Spinal Cord, Arch. Neurol. & Psychiat. **21**:1331 (June) 1929.

16. Selinsky, Herman: Adhesive Spinal Arachnoiditis with Marked Improvement Following Laminectomy and Radiotherapy, J. Mt. Sinai Hosp. **1**:84, 1934.

17. Oesterreicher, M.: Arachnoiditis fibrosa spinalis luetica unter dem Bilde des Pseudotumors, Jahrb. f. Psychiat. u. Neurol. **49**:57, 1933.

cases reported here the results of serologic tests were negative. In one instance the spinal fluid was xanthochromic, and in another there was pleocytosis of mononuclear elements. Metzger also reported that abnormalities in the protein and cellular content may be noted. Stookey mentioned that in a number of cases which he studied a history of some antecedent infection was elicited. In the series here reported, five patients had pneumonic or pleuritic infections (cases 4 to 8, inclusive); one patient was subject to repeated attacks of tonsillitis (case 1), and another had diseased teeth (case 2). Several of the patients had had gonorrheal infection at some time before coming under observation. The appearance of neural symptoms in the case of a diabetic patient was ushered in by an attack of grip with pulmonic involvement. The not infrequent association of spinal arachnoiditis with arthritis has already been mentioned. The theory of focal infection may be entertained here also, as in the case of nonspecific inflammatory diseases. There was no evidence of tuberculosis in any of the cases to be reported. The variety of associated conditions which may be related to spinal arachnoiditis indicates that this condition is not a specific response of the leptomeninges to a single causative agent but may be caused by any one of a variety of agents which are capable of producing a reactive inflammation of the pia-arachnoid.

ANATOMIC CONSIDERATIONS

The outer tough dura, which is fibrous, contains the leptomeninges (the pia and the arachnoid), membranes that are rather delicate and intimately associated with each other. They take origin from the inner layer of the primitive mesenchyme. As further differentiation and separation of these membranes occur the fenestrated mesenchymal meshwork that connects them develops into trabeculae. These trabeculae are therefore remnants of the numerous septums which existed before the increasing mechanical distention of the subarachnoid space by the newly-formed cerebrospinal fluid forced the potential space into actual being.

The arachnoid membrane itself possesses no capillaries, but the vascular supply to the spinal cord, a rich network of small arteries and veins, courses along the trabeculated stroma of the pia-arachnoid. These vessels thus receive a joint covering of stroma and mesothelial cells from the pia and the arachnoid and lie in the subarachnoid space. Similarly, the spinal roots become covered with mesothelium as they emerge from the spinal cord proper.

The exact morphologic and physiologic relationship between the arachnoid, as a perineural sheath, and the root has been a matter of

controversy. Elman [18] did not find evidence in his dye experiments to substantiate the contention of Cathelin [19] and Weigeldt [20] that an anatomic continuity exists between the subarachnoid space and the perineural lymphatic system. Basing his conclusions on the presence of arachnoidal mesothelial clusters, he stated that it is these clusters that serve as a means for the physiologic transmission of fluids from the subarachnoid space into the tissues around the nerve roots, including the lymphatic system. Weed [21] injected an isotonic foreign solution into the lumbar subarachnoid space and observed that this substance passed into the venous sinuses by way of the arachnoidal villi. Key and Retzius [22] stated that definite pathways exist by which cerebrospinal fluid escapes into the substance of the nerves as well as into the perineural spaces. These observations were based on the injection of solutions of gelatin containing berlin blue (tri-phenylrosaniline hydrochloride) into the subarachnoid space. The blue color extended outward along the spinal nerves for a considerable distance from the cord. Hassin [23] has recently asserted his belief that transmission of the cerebrospinal fluid occurs from the spinal subarachnoid space to the perineural spaces of the spinal roots.

In a number of cases I have observed that when india ink had been injected into the subarachnoid space at autopsy, after the thoracic and abdominal organs had been removed, the dye was seen to be seeping into the thoracic cavity by way of the intercostal apertures at the costovertebral junction. This rough observation is restricted by obvious limitations, but in view of Orr's [24] work on ascending pathways of infection from seats of inflammation outside the spinal subarachnoid space one might formulate a hypothesis about the relationship of intrathoracic infection to the subsequent development of spinal arachnoiditis. This hypothesis is further strengthened by Pette's [25] statement that con-

18. Elman, R.: Spinal Arachnoid Granulations with Especial Reference to the Cerebrospinal Fluid, Bull. Johns Hopkins Hosp. **34**:99, 1923.

19. Cathelin, F.: La circulation du liquide cephalorachidien, avec applications à la thérapeutique, Paris, J. B. Baillière et fils, 1912.

20. Weigeldt, W.: Regelmässige Unterschiede in der Zusammensetzung des Liquors an verschiedenen Stellen des Subarachnoidealraumes, München. med. Wchnschr. **68**:838, 1921.

21. Weed, Lewis H.: The Cerebrospinal Fluid, Physiol. Rev. **2**:171, 1922.

22. Key and Retzius, cited in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1928, vol. 2, p. 614.

23. Hassin, G. B.: So-Called Circulation of the Cerebrospinal Fluid, J. A. M. A. **101**:821 (Sept. 9) 1933.

24. Orr, David W.: Pathways of Infection to the Central Nervous System, A. Research Nerv. & Ment. Dis., Proc. **12**:88, 1931.

25. Pette, H.: Ueber localisierte, unter dem Bilde eines raumbeschränkenden Prozesses verlaufenden Spinalmeningitis, Arch. f. Psychiat. **74**:631, 1925.

ceivably a transient bacterial invasion of the subarachnoid space may occur which is limited by the bactericidal powers of the cerebrospinal fluid. Moreover, it has been shown by Flexner and Amoss that in the monkey invasion of the cerebrospinal fluid by a virus can be demonstrated to be transitory.

PATHOLOGY

The gross features of the pathologic process consist of thickening and adhesions of the arachnoid membrane, which vary in degree and extent. Occasionally, when a probe is passed into the subarachnoid space an obstruction is encountered, marking the location of adhesions. Retardation of the free flow of cerebrospinal fluid also is noted. The thickening of the arachnoid can sometimes be seen with the naked eye as a series of dense bands, and not uncommonly the roots appear reddened. At times cystlike accumulations of fluid are found in the areas where the adhesions are firm. Again, the adhesive process may be restricted to the zone where the root emerges from the spinal cord, so that on casual inspection no gross obstruction is apparent. Thinning and pallor of the spinal cord, with strangulation of the blood vessels, may sometimes be observed.

Keschner and Davison [26] described adhesions of the meninges and narrowing of the blood vessels in a woman, aged 52. A meningioma had been removed from the thoracic region of the cord in 1917, and the patient had been well until 1927, when signs of compression of the cord reappeared. Laminectomy revealed meningeal adhesions but no tumor, and this condition was confirmed at necropsy. A similar case has come under my observation, that of a woman, aged 66, who had been subjected to laminectomy in 1925, with removal of an extramedullary endothelioma at the level of the first thoracic roots. After the operation there was recovery of function. The patient returned in 1930 with recurring signs of compression of the cord. The Queckenstedt test revealed no abnormality, and she was discharged for further observation. In 1931 laminectomy was again performed, with the discovery of arachnoid adhesions pulling the cord over to one side sharply. There was no evidence of tumor. The blood vessels were somewhat dilated.

The microscopic appearance of a specimen of tissue removed at operation (fig. 1) is characterized by productive thickening and infiltration of the leptomeninges. The changes involve the entire pia-arachnoid. The question may therefore be raised as to the propriety of the term disseminated arachnoiditis. Disseminated leptomeningitis would be more accurate, but it is probably unwise to make a change

26. Keschner, Moses, and Davison, Charles: Myelitic and Myelopathic Lesions, Arch. Neurol. & Psychiat. **30**:592 (Sept.) 1933.

in terminology at present. One should, however, recall that a century ago the term arachnoiditis [27] was used to designate a condition that today is classified as suppurative meningitis.

ROENTGEN THERAPY

The amelioration of pain which high voltage roentgen therapy has so often effected in cases of painful lesions of the spinal cord and

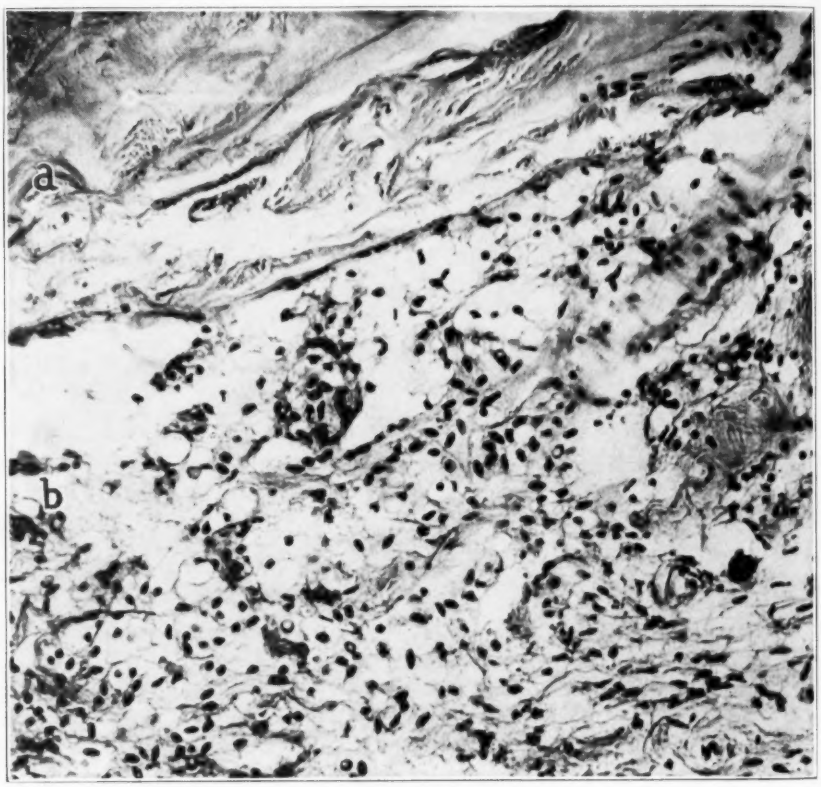

Fig. 1.—Section of a specimen removed at laminectomy, showing productive thickening of the pia-arachnoid and mononuclear infiltration within the meshes of the leptomeninges (magnification, × 280); *a*, the dura mater; *b*, the leptomeninges.

roots, e. g., in syringomyelia and malignant disease of the bones, led to the use of this treatment in cases of spinal arachnoiditis. The treatment can be repeated at intervals, as the situation warrants, over an extended period of time. In my experience no other nonsurgical therapeutic measure has exerted such a favorable influence in this condition.

27. Feraud, S. H. H.: Essai sur l'arachnoïdite, Thèse de Paris, no. 82, 1824.

The technic of the treatment (which is given under the direction of Dr. William Harris [28]) may be outlined as follows:

The spine is cross-fired with high voltage roentgen radiation at the various levels indicated by the sensory disturbance. One or more series of treatments are given, depending on the response to the therapy. If indicated, the series of treatments is repeated at intervals of six weeks.

Fractional treatments are given at each sitting and consist of from 100 to 150 roentgens (in air) until a total of 800 roentgens is administered. The factors used are: (180 kilovolts, a filter of 0.5 mm. of copper and 1 mm. of aluminum, 4 milliamperes and a focal skin distance of 40 or 50 cm.).

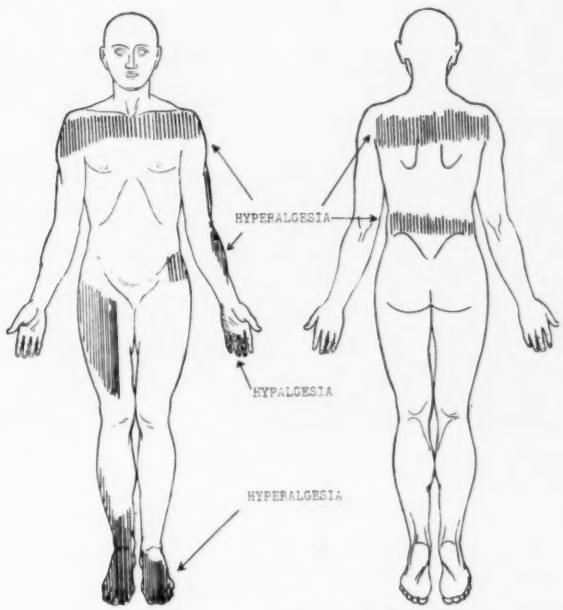

Fig. 2.—Diagram illustrating the salient features in case 1.

REPORT OF CASES

CASE 1.—M. C., a nurse aged 27, was first seen in September 1928 for the complaint of shooting pains in all the extremities and the face, which had arisen gradually during the past one and one-half years. She had suffered repeatedly from tonsillitis.

The findings on admission consisted of zones of hyperalgesia, radicular in pattern (as charted) and a change in the deep reflexes (fig. 2). The right ankle and knee jerks were more active than those on the left. There was weakness of the left upper and lower extremities. No signs suggesting involvement of the pyramidal tract were present. The Queckenstedt test showed the presence of a

28. Selinsky, Herman, and Harris, William: Radiotherapy in Disseminated Spinal Arachnoiditis, New York State J. Med. **34**:85, 1934.

partial block of the spinal fluid. Iodolography, performed by the cisternal injection of iodized poppy-seed oil 40 per cent, revealed an arrest of oil droplets as shown in the roentgenograms (fig. 3).

The treatment first given included the use of analgesics and foreign protein. Very little change was noted by the patient or by the examining physician. After a course of high voltage roentgen therapy, the patient obtained striking relief from pain, and when the pain recurred in 1931 repetition of the roentgen therapy caused its complete disappearance.

The patient is now working actively and has no discomfort. On recent examination there were areas of hyperalgesia at the level of the eighth cervical and first dorsal roots on the left and from the fifth lumbar to the third sacral root bilaterally.

CASE 2.—Morris C., a man aged 59, gave a history of gonorrheal infection on two occasions in 1902 and 1919. He was first admitted to the service of Dr. Israel Strauss in 1927, with a history of pain in the legs six years before, which had been relieved by the removal of diseased teeth. At the time of admission he was

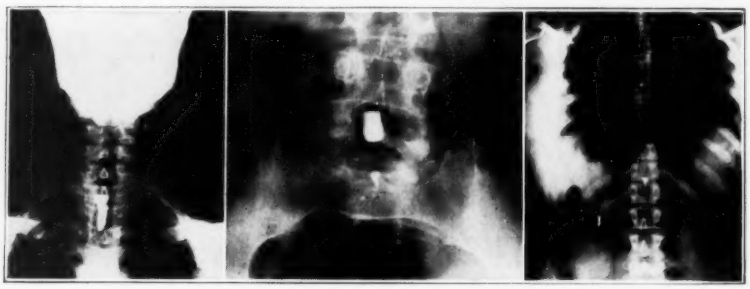

Fig. 3.—Roentgenogram demonstrating the various levels of arrest of the iodized oil in case 1.

suffering from a return of the pain in the left lower extremity, for which three epidural injections had been given without relief.

Examination on admission, on Aug. 25, 1930, showed a zone of hyperesthesia at the level of the twelfth dorsal and first lumbar roots on the left, hypalgesia in the fifth lumbar and first dorsal roots on the left, a diminution of the reflexes in the left iliac region, a diminished achilles tendon jerk on the left and a Lasègue sign bilaterally (fig. 4). A Queckenstedt test (1927) showed a questionable delayed rise and fall of the cerebrospinal fluid pressure which was not confirmed by a subsequent test (1930). Iodolography showed an arrest of the oil (fig. 5). Immediately following this procedure the patient complained of exacerbation of pain in both lower extremities. Laminectomy was performed by Dr. Harold Neuhof, and a bony prominence was revealed at the level of the second lumbar vertebra, which was interpreted as an osteoma. However, no specimen was obtained for histologic study. After the operation the patient noted definite symptomatic improvement. Three years later, in 1930, a return of pain in the lumbar region compelled him to enter the hospital again for treatment. The Queckenstedt test showed no evidence of a block; the spinal fluid was clear and contained 2 cells. The patient was treated with salicylates, baking and diathermy, and these measures afforded moderate relief. In 1931 he came to the outpatient department complaining of burning pain in the back and a cramplike burning sensation in

both feet. It was suspected that he might have arachnoiditis, and he was referred for roentgenographic examination of the spine. A scattering of iodized oil was visualized, which confirmed the clinical impression of arachnoiditis. High voltage

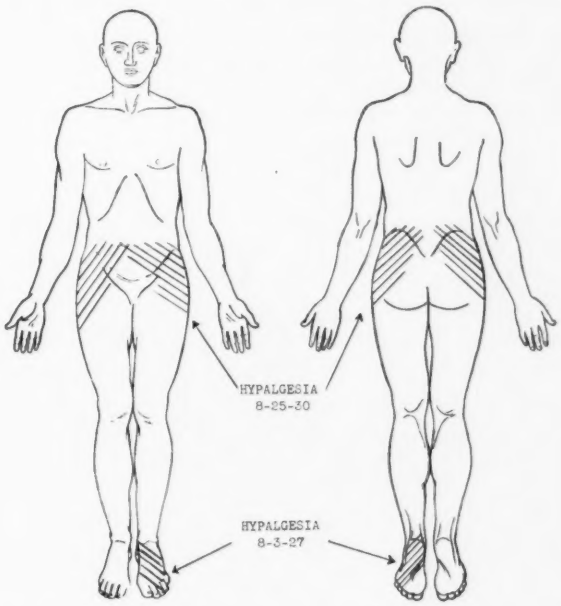

Fig. 4.—Diagram illustrating the salient features in case 2.

Fig. 5.—Roentgenogram demonstrating the arrest of the iodized oil in the lumbar subarachnoid space in case 2.

irradiation resulted in complete cessation of pain. The patient returned in March 1932, because of a recurrence of cramplike burning pain in the left foot. He was given a second course of treatment and suffered only one attack of pain in the

subsequent six months. The objective sensory findings at present do not show any deviation from the normal. However, the diminished achilles tendon jerk on the left side is still present.

CASE 3.—Jack S., aged 49, was admitted to the service of Dr. Strauss in 1928, complaining of pain in the lumbar region and in both lower extremities for five months. Appendectomy had been performed one year previously.

Examination showed the absence of the knee jerk on the left, some atrophy with fibrillation of the left lower extremity and diminution of all forms of sensation, as illustrated in the diagram (fig. 6). A Queckenstedt test indicated the presence of a partial block of the cerebrospinal fluid. Iodolography revealed arrest of the oil droplets at the level of the third and fourth dorsal vertebrae and again at the level of the fourth and fifth lumbar vertebrae (fig. 7).

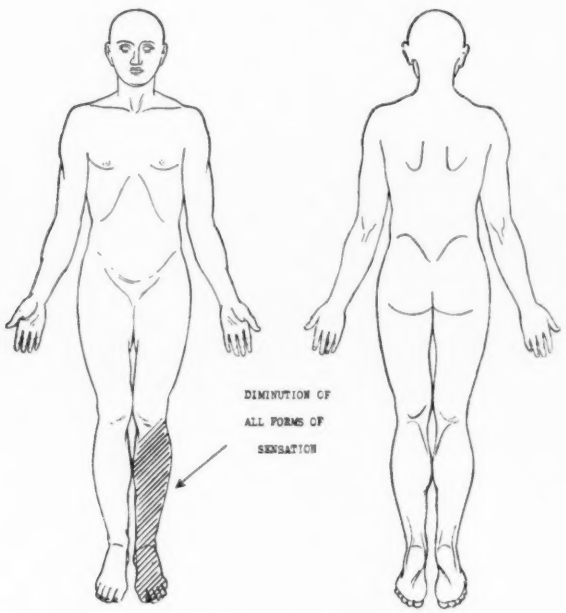

Fig. 6.—Diagram illustrating the salient features in case 3.

Laminectomy was performed by Dr. Charles A. Elsberg, who observed that the roots and exposed portion of the spinal cord were reddened and inflamed and made an operative diagnosis of arachnoiditis with lumbosacral radiculitis.

After laminectomy the patient received diathermy treatment, with slight relief from pain.

In 1930 the patient came to the outpatient department, complaining of burning pain in the lumbar region, radiating down from both legs and across the shoulders. Again, the peculiar type of pain led the examiner to suspect the presence of arachnoiditis, but he was unaware that the same diagnosis had been made in the hospital two years before. High voltage roentgen treatment gave gradual relief from pain. The patient volunteered the statement that nothing that he had tried in the preceding two years had helped him as much as roentgen therapy. The pain recurred in April 1931 and was promptly relieved by another course of irradiation.

The physical findings at present consist of evidence of mild lumbosacral radiculitis in the left lower extremity.

CASE 4.—Joseph E., aged 52, was first admitted to the service of Dr. Strauss in March 1926, complaining of pain in the right hip radiating down the thigh for five months. In 1918 he was ill with "influenza and pneumonia."

Examination in May 1927 revealed atrophy and fibrillation of both lower extremities, a Lasègue sign bilaterally and sensory changes in both lower extremities indicating radicular involvement (fig. 8). The Queckenstedt test revealed no abnormality, although the spinal fluid was slightly xanthochromic. Iodolography disclosed an arrest of droplets throughout the lumbar subarachnoid space, with a massive arrest at the third lumbar vertebra (fig. 9*A*).

Laminectomy was performed by Dr. Elsberg, who noted the presence of gross alterations indicative of arachnoiditis and neuritis of the cauda equina.

For eight months after the operation the patient felt much better. At that time, however, recurrence of pain prompted the use of high voltage roentgen

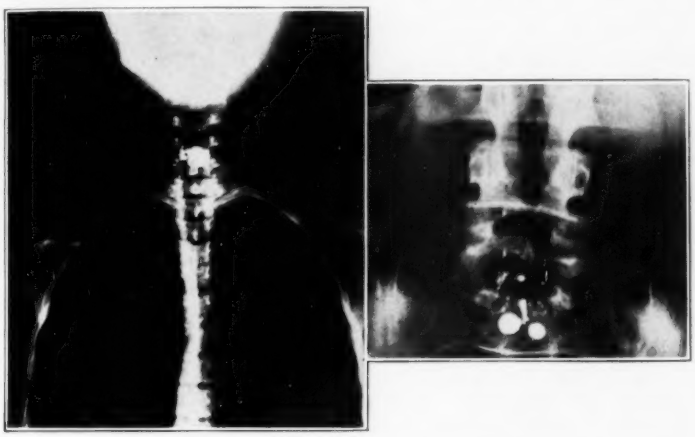

Fig. 7.—Roentgenograms demonstrating the various levels of arrest of the iodized oil in the cervicodorsal and lumbar regions in case 3.

therapy. Relief was gradually obtained, so that the patient could sleep through the night without being awakened by pain. At present, however, he has some pain in the lower extremities, and there is a saddle-shaped area of hyperalgesia in the sacral dermatomes. There was no history of sphincteric disturbance, nor has there been any impairment of motor power.

CASE 5.—Joshua A., aged 36, gave a history of "pleurisy with pneumonia" in 1925 and 1926.

Examination on Nov. 21, 1927, showed that the abdominal reflexes were absent; the left knee jerk was diminished and the ankle jerks were active. There was no Babinski sign.

He was admitted to the service of Dr. Strauss in December 1929, complaining of pain in the right lower extremity. He had been treated in the hospital twice previously for epigastric pain, pains in the lower part of the back and frequent frontal headache, for which no adequate cause was found.

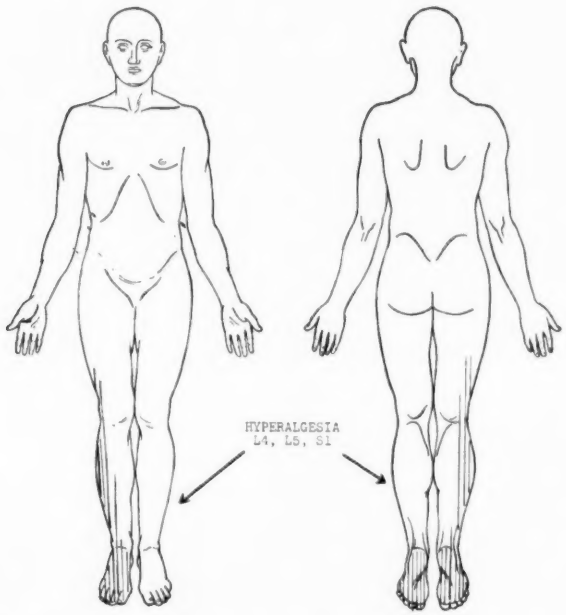

Fig. 8.—Diagram illustrating the salient features in case 4.

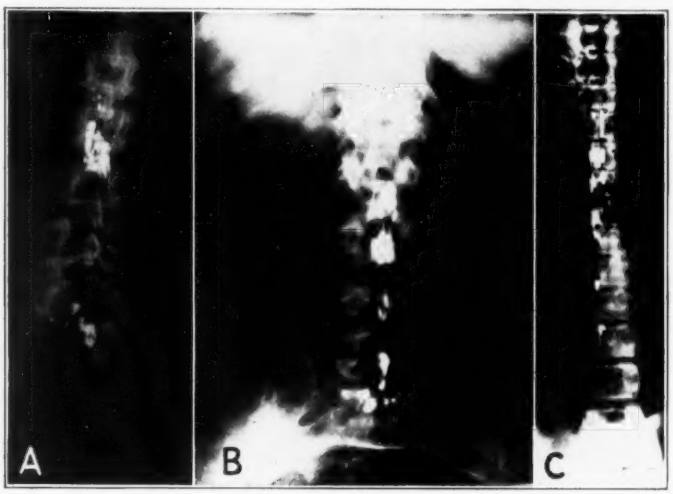

Fig. 9.—*A*, roentgenogram demonstrating the arrest of the iodized oil in the dorsolumbar region in case 4; *B*, in the lumbar region in case 6; *C*, in the thoracic region in case 7.

On examination there were tenderness over the right sacro-iliac region and sensory disturbances, as charted (fig. 10). The abdominal reflexes were present; the knee jerks were diminished; there was a Lasègue sign on the right, and the plantar responses were normal. Roentgen examination of the spine and sacrum revealed no abnormality. The Queckenstedt test gave no evidence of block; the spinal fluid was clear, and only 6 cells were present. Iodolography showed an arrest of the oil in the cervical subarachnoid space. Unfortunately the plates are not now available. The patient received treatment with salicylates, baking and an orthopedic support for the back but did not experience sustained improvement.

In the spring of 1930 high voltage roentgen therapy afforded great relief, so that the patient could walk with comfort. Since the first course two additional courses, prompted by a recrudescence of pain in both extremities, have been given.

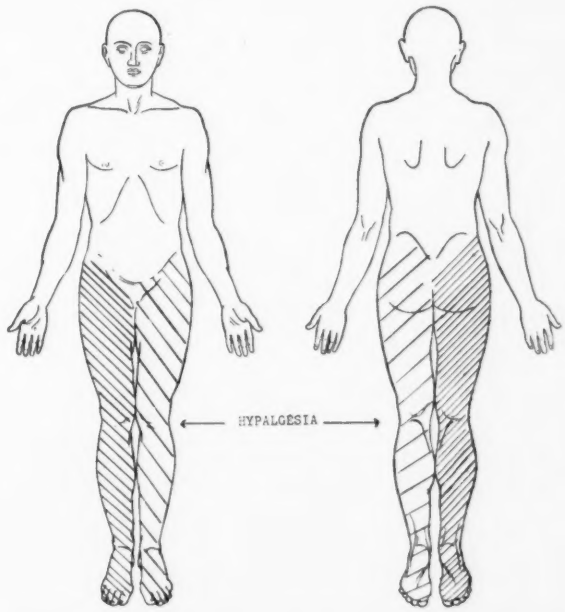

Fig. 10.—Diagram illustrating the salient features in case 5.

This measure has again acted favorably in alleviating discomfort, so that the man is able to work.

The only positive finding at present is an occasional sensory change at the level of the fourth dorsal vertebra.

CASE 6.—Sam S., aged 45, was admitted to the service of Dr. Strauss on Aug. 29, 1927. He had had gonorrhea at the age of 25, a cholecystectomy at 35 and pneumonia at 39. About nine months prior to admission he experienced pain in the back and chest, with stiffness of the neck. The pains gradually disappeared in two months with rest. About two and a half months previous to coming to the hospital the patient began to suffer constant pain in the back of the right leg, which started in the foot and ascended to the thigh. He also experienced numbness of the right foot. Those symptoms persisted in spite of rest and physical therapy.

On his admission neurologic examination revealed hyperactive knee and ankle jerks, the right being more active than the left; hypalgesia and hypothermesthesia over the region supplied by the fifth lumbar and first sacral roots; impairment of the vibratory and joint position senses in the right foot; tenderness in the lumbosacral region, and a guarded gait (fig. 11). The Queckenstedt test revealed a partial block; the fluid was clear and contained 53 cells (97 per cent mononuclears). Iodolography showed arrest of the oil in the lumbar subarachnoid space and moderate spondylitis (fig. 9 *B*).

Laminectomy did not reveal any gross pathologic change.

The condition improved after the operation. There was a recurrence of pain in the lower part of the back two years later, with the addition of pain in the

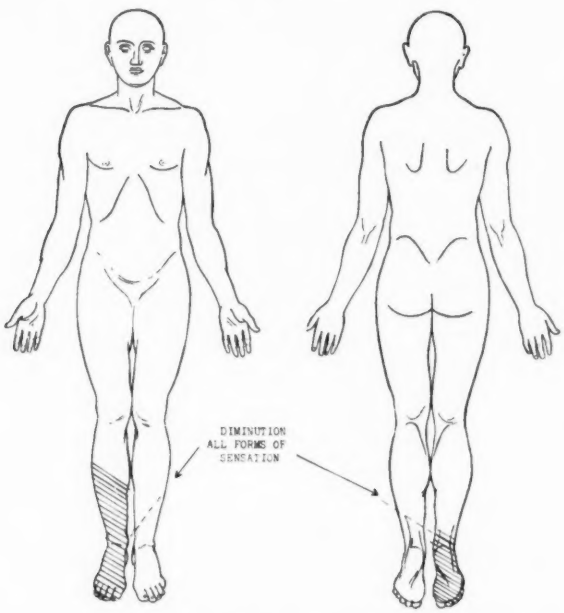

Fig. 11.—Diagram illustrating the salient features in case 6.

left leg; this pain persisted, and in September 1931 the patient was readmitted. No sphincteric disturbance was reported. The left knee jerk was less active than the right. The right ankle jerk was not elicited. Fascicular twitchings of both calves were observed, with vague sensory disturbances. The patient left the hospital against advice before further data could be obtained.

CASE 7.—This case report is included by way of contrast, as the typical syndrome of compression of the spinal cord described by Stookey was manifest. Patients with this syndrome always should be subjected to exploratory laminectomy in an attempt to discover a gross remediable lesion.

Frank H., aged 47, had "pleurisy pneumonia" in 1923 and in the same year was treated for gonorrhea. The patient began to suffer from blurring of vision and vertigo five years before admission to Dr. Strauss' service in 1929. These symptoms disappeared, but he then began to notice stiffness and numbness of the

left foot; two years prior to admission the right leg became affected. There were also urinary frequency and on several occasions incontinence. Also there had been pain in the lower part of the back.

Examination on admission showed inequality of the size of the pupils, the right being sluggish; spasticity of both legs; bilateral signs of involvement of the pyramidal tract below the waist, and sensory impairment up to the level of the fifth and sixth dorsal vertebrae (fig. 12). The Queckenstedt test showed a complete block. Serologic tests gave negative results. Iodolography was performed, and a scattered arrest of oil was observed in the dorsal subarachnoid space between the fourth and the eighth dorsal vertebra (fig. 9*C*).

Laminectomy revealed an adherent arachnoiditis, with thinning of the cord in the middorsal region. The surgical pathologic report indicated the presence of a

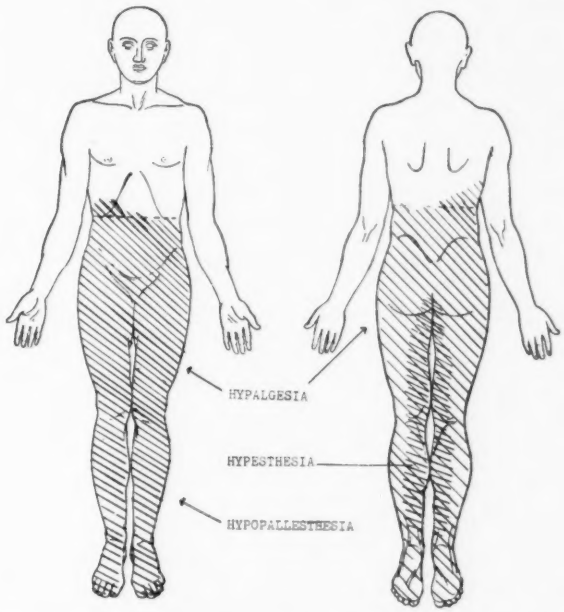

Fig. 12.—Diagram illustrating the salient features in case 7.

subacute productive leptomeningitis. Antisyphilitic therapy was administered, although serologic tests had been negative. The condition has shown little improvement since. No roentgen therapy has as yet been administered.

CASE 8.—Through the courtesy of Dr. Emil Altman, I saw P. W., a man aged 62, who had been admitted to another hospital because of complaints of weakness in the left hand for four months, pain in the shoulders, staggering gait for five weeks and pains radiating up and down the legs for about two weeks. He had been known to be diabetic for five years.

Examination revealed weakness, flaccidity and diffuse atrophy in the muscles of the extremities. There was loss of vibratory perception below the level of the fourth dorsal roots with areas of hypalgesia in the lower extremities, extending up to the level of the third dorsal roots. The deep reflexes were not elicited in

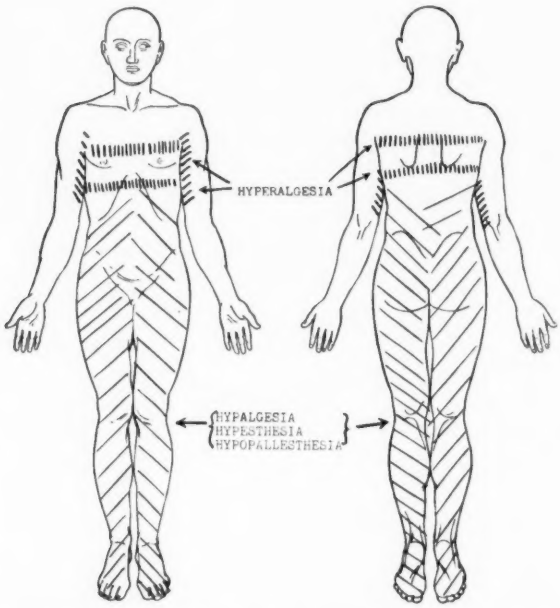

Fig. 13.—Diagram illustrating the salient features in case 8.

Fig. 14.—Roentgenogram demonstrating the arrest of the iodized oil in the cervicothoracic subarachnoid space in case 8.

either the upper or the lower extremities. Zones of hyperalgesia were found at times at the levels of the sixth, eighth and second dorsal roots (fig. 13). There was no sphincteric impairment. Roentgen examination of the spine revealed fairly marked spondylitis, particularly in the cervical region. The Queckenstedt test revealed a partial block, and after iodized oil was injected cisternally various levels of arrest of the oil were noted (fig. 14). A short course of high voltage roentgen treatment was given in the cervicodorsal region, and the patient was placed under a diabetic regimen (diet and insulin) and slowly improved. In this case there was evidence of mild involvement of the spinal cord, roots and peripheral nerves. The various levels of hyperalgesia suggested the presence of disseminated spinal arachnoiditis, which was confirmed by the iodologram. It should be emphasized that there was evidence of marked spondylitis in the cervical region.

Comment.—In cases 1, 3, 6 and 8 a partial block was revealed by the Queckenstedt test; in case 7 there was a complete block, as would have been expected. In case 2 a questionable block was noted on the first admission, but the Queckenstedt test revealed no abnormality on the second admission. It is noteworthy that in case 4, in which the Queckenstedt test showed no evidence of block, slightly xanthochromic spinal fluid was obtained. In all the cases reported there was a scattered arrest of iodized oil after cisternal injection. Again it is pointed out that most of these patients had suffered from some form of pleurisy or pneumonia.

SUMMARY

Eight cases are presented in which a syndrome characterized by "burning" pain in one or more extremities for several months was noted. The objective signs pointed to a polyradicular process, infrequently associated with signs of disease of the spinal cord.

The Queckenstedt test and iodolography are indispensable aids in leading to a correct diagnosis in cases of disseminated spinal arachnoiditis.

The etiology of this condition is unknown, but there is some evidence to suggest an extension of a focal infection.

High voltage roentgen therapy exerts a definitely ameliorating effect, which is variable in duration. Recurrence of pain is usually relieved by a repetition of the roentgen treatment.

VASCULAR CHANGES FOLLOWING EXPERIMENTAL LESIONS IN THE CEREBRAL CORTEX

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CHICAGO

There are at least three possible causes of disturbances of behavior after an injury to the cerebral cortex. First, the functional organization may be disturbed by direct damage to the nerve elements involved. Second, the destruction of cells in one region may result in functional disturbances in cells in other regions by diaschisis. Third, the metabolism of adjacent or even remote parts may be disordered by alteration of the vascular supply. Vascular changes may not coincide with the region of direct damage to nerve cells. In general, vascular deficiency in a cortical field always implies functional abnormality, although a functionally abnormal area does not necessarily mean the presence of vascular disturbance. In the case of a lesion with actual removal of tissue, there is always a zone bordering the site of the operation in which both cellular and vascular changes are apparent. The present study was made in an attempt to determine the relative extents of the two disturbances after a lesion is inflicted on a cortical field and to discover whether vascular changes sufficient to account for functional disturbance can be demonstrated at greater distances from the site of operation.

This problem is of considerable theoretical and methodologic importance. In explaining how local injuries may produce general symptoms, Piéron [1] stressed the disturbance of the neuronic metabolism as an effective cause of the disturbance of cellular activity of the entire brain in that metabolic changes reduce the energy of discharge of the cells or their capacity to recover from fatigue. Buytendijk [2] held the circulatory disturbances following cauterization of cortical tissue to be partially responsible for the detrimental effect on behavior. He also contended that after cauterization substances of decomposition are formed, which are cell poisons able to cause edema in adjoining tissue. Through the circulatory system the poisonous effects may be carried to remote parts of the brain.

From the psychologic laboratory, the University of Chicago.

1. Piéron, H.: Le cerveau et la pensée, Paris, Masson & Cie, 1923.

2. Buytendijk, F. J. J.: An Experimental Investigation into the Influence of Cortical Lesions on the Behaviour of Rats, Arch. néerl. de physiol. **17**:370, 1932.

Lashley [3] regarded it as improbable that the metabolism of cells remote from the lesion can be affected permanently. He noted the perfect normality of the cortex, even at the edge of a lesion, without evidence of shrinkage or changes in the cellular appearance. Thus, structural defects are not present where metabolic disturbance is most likely to be expected. The possible effects on behavior of the chemical disturbances from the presence of necrotic tissue are eliminated by the fact that deterioration in maze-learning ability persists for at least three months. He [4] also produced artificial dilatation of the ventricles in the rat and found that this condition, assumed by others to involve metabolic disturbances, had no effect on efficiency in the maze. Lashley and Frank [5] destroyed regions adjacent to the striate area and parts of the area itself in the rat. Visual habits of discriminating patterns were not disturbed so long as a part of the binocular projection field was spared. The inference was that trophic disturbances sufficient to interfere with the function of the sensory fields are not usually produced by injuries adjacent to the fields.

The possibility remains, however, that trophic disturbances may affect one type of function more seriously than another and that although the sensory functions of a projection area may be unaffected by an adjacent lesion, the more general integrative functions, such as were indicated in the study of the nonvisual functions of the visual cortex (Tsang [6]) may suffer.

In spite of the importance of the rôle of the vascular system in transporting food, metabolites, toxins, etc., following a cortical lesion, no attempt has been made to demonstrate directly the nature of the vascular disturbance after a restricted injury to the cortex.

The effects of cortical injury have been enthusiastically studied in the past two decades, especially in the rat. For a reconstruction of the lesion, the criteria usually employed are the absence, degeneration and disorganization of the nerve elements. If the vascular disturbances from an injury were more extensive than the cyto-architectural disturbances the lesion as reconstructed would be smaller than the actual

3. Lashley, K. S.: Brain Mechanisms and Intelligence, Chicago, University of Chicago Press, 1929.

4. Lashley, K. S.: Studies of Cerebral Function in Learning: X. The Effects of Dilation of the Ventricles upon Maze-Learning, Am. J. Physiol. **104**:51 (April) 1933.

5. Lashley, K. S., and Frank, M.: The Mechanism of Vision: X. Post-Operative Disturbances of Habits Based on Detail Vision in the Rat After Lesions in the Cerebral Visual Areas, J. Comp. Psychol. **17**:355 (June) 1934.

6. Tsang, Y. C.: The Functions of the Visual Areas of the Cerebral Cortex of the Rat in Learning and Retention of the Maze: I., Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1934, vol. 10, no. 4.

zone of disordered function. Therefore, from a purely methodologic standpoint, study of the relative extent of the vascular and the cyto-architectural disturbance following a cortical lesion answers a real need.

METHODS

In estimating the possible vascular disturbance following a cortical lesion there are at least six factors to be considered: the locality of the lesion, its size, shape, depth and age and the means used to inflict the injury. With these factors in view, I tested the relative extent of the vascular and the cyto-architectural changes following a cortical wound. I selected the rat as the subject and inflicted injuries of different size, shape and depth in different regions of the cortex. After a definite interval a contrast subject was injected into the blood vessels of the brain. The extent of the cyto-architectural disturbance was determined by histologic criteria.

The operation was done with the animal under deep anesthesia with ether. The selected spot of the cerebral cortex was destroyed through an opening in the skull. Three types of instrument were used to make the lesions: the electric thermocautery, the trephine and the needle. An attempt was made to avoid the subcortical structures. The animal was kept in the aboratory under sanitary conditions until the time for injection.

After a definite interval following the operation a mixture of carmine and gelatin prepared according to Bensley's process was injected into the brain of the animal. With the animal under anesthesia a small cannula connected with the injection set was inserted into the ascending aorta through the left ventricle of the heart. Physiologic solution of sodium chloride, together with a small dose of sodium nitrite, was first injected to wash out the blood and dilate the capillaries. The warmed carmine-gelatin mixture was next injected. A tough cord was passed through the deep tissues of the neck and above the ascending aorta and tied. The head was cut off and dropped into a dilute solution of formaldehyde U. S. P. (1:10) for twenty-four hours to fix the brain in situ.

The brain was removed from the skull, and a rough free-hand drawing was made of the lesion to show its topographic position and its relation to the large blood vessels. The brain was then prepared for sectioning. Pyroxylin sections of 50 microns were cut and stained very lightly with thionine. The lesion of each rat was reconstructed on Lashley's diagram of the rat's cerebrum (fig. 1). The size of the lesion was measured and expressed as the percentage of the total surface area of the neopallium.

EXPERIMENTAL DATA

All the rats used in this study were females. They were at adult age, from about 100 to 150 days, at the time of operation. For the experimental animals separate protocols were kept, which are summarized in the table. To show the general features of the vascular supply of the neighboring parts of the lesion, two photomicrographs of representative sections from 2 animals (rats 2 and 3) are reproduced in figure 2. The jagged margin marks the site of the lesion, the boundaries of which are indicated by arrows. For the present purpose the fine capillaries are more significant than the large vessels. Camera tracings are better than photographs in showing the finest capillaries, and tracings for rats 2a and 9b (figs. 3 and 4) are presented.

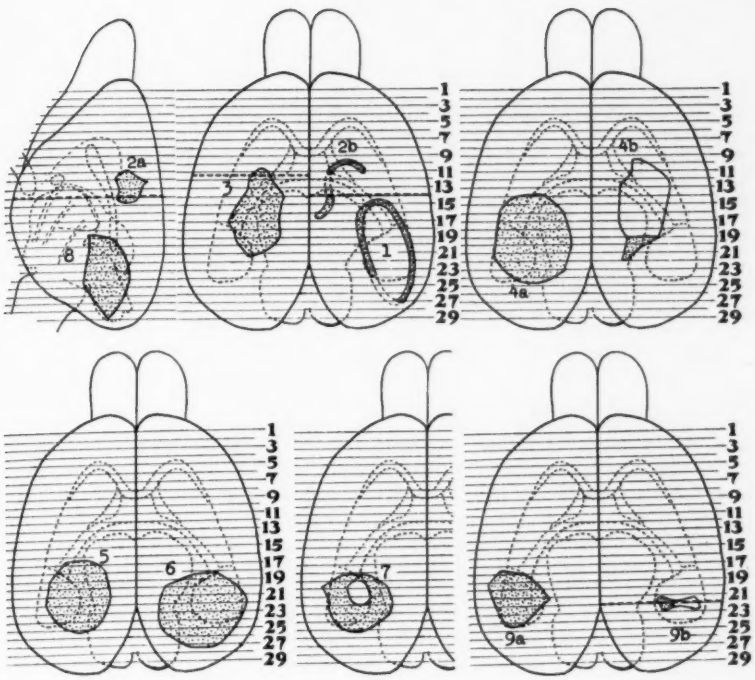

Fig. 1.—Reconstructions of the cortical lesions in the experimental animals. The heavy broken lines across the lesions in rats 2a, 2b, 3 and 9b indicate the levels at which representative sections were selected for the photomicrographs and camera tracings of the blood vessels. In those parts marked by broken lines in rats 1 and 2b, there was no actual loss of tissue, only traces of mechanical pressure being recognizable. The light part in rats 4b and 9b indicates the site of the undercut.

Records of the Experimental Animals *

No.	Variety	Body Weight at Necropsy, Gm.	Cortical Areas Involved	Size of Lesion	Shape of Lesion	Depth of Lesion	Time Interval, Days	Kind of Operation	Vascular Condition
1	Hooded	179	R: j, w, p	1.5	Horseshoe-shaped	I–VI	10	Trephine	Normal
2	Hooded	184	(*a*) L: j (*b*) R: j, f, m′, aa	0.9 0.8	Roundish S-shaped	I–II I–V	11	Cautery Needle	Increased Increased
3	Albino	170	L: j, w, n	3.4	Pear-shaped	I–V	20	Cautery	Increased
4	Albino	156	(*a*) L: j, p, w, m′, n (*b*) R: j, n, w	6.2 4.1	Round Undercut	I–VI Corpus callosum	20	Trephine Needle	Increased Normal
5	Hooded	255	L: j, w	4.2	Round	I–VI	53	Trephine	Increased
6	Black hooded	207	R: m′, w, p	6.0	Round	I–VI	72	Trephine	Normal
7	Hooded	221	L: w, p	2.8	Ring-shaped	I–VI	73	Cautery	Increased
8	Black hooded	198	L: w, p	3.3	Rhomboid	I–VI	73	Cautery	Increased
9	Hooded	198	(*a*) L: w, p (*b*) R: w	2.6 0.4	Roundish Undercut	I–VI IV	95	Trephine Needle	Increased Increased

* In the fourth column R means the right and L the left hemisphere; the small letters are Fortuyn's cortical areas. The size of the lesion is expressed as the percentage of the total cortical surface. Brodmann's terminology is used for the cortical layers to express the depth of the lesion. The time interval is that between the operation and the injection. The last column indicates the vascular condition of adjoining parts of the lesion.

RESULTS

On the whole, the injections were successful, but not to the same degree in all cases. The condition in each experimental animal differed from that in the others in more than one respect, but the results were essentially the same. The tissues adjoining the lesion were increased in vascularity in most animals. The increase was indicated

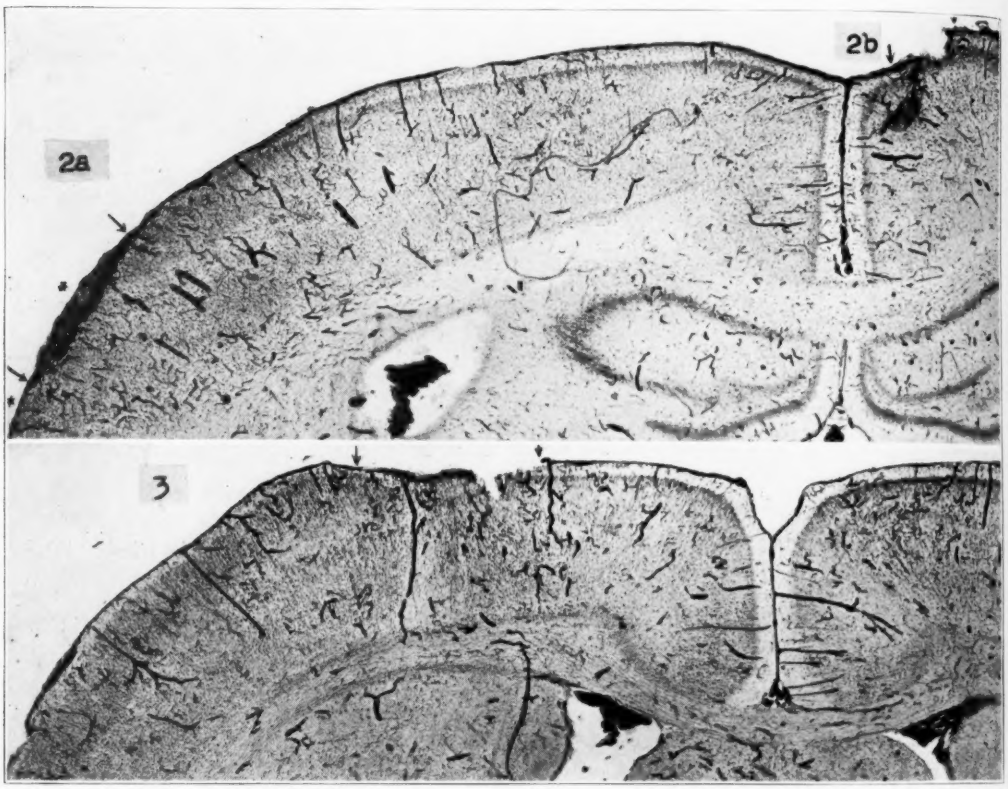

Fig. 2.—Photomicrographs of transverse sections, 50 microns thick, through the brains of rats 2 and 3, showing the vascular condition in and around the lesions (between the arrows). The levels at which these sections were taken are indicated by broken lines drawn across the respective reconstructed lesions in figure 1. Protocols of these animals are summarized in the table. Carmine-gelatin injection; magnification, × 20.

by one or more of three changes: (1) a greater number of blood vessels, (2) a larger caliber of feeding vessels and (3) richer capillary anastomoses. In no animal was the vascularity of the parts below normal. A thick mass of blood vessels usually extended to the very margin

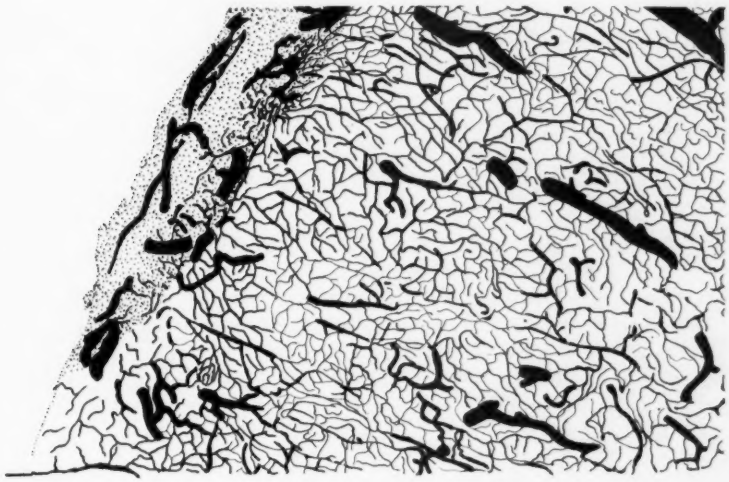

Fig. 3.—The vascular condition in and around the ventral corner (between the stars in fig. 4) of the lesion in rat 2a. The dotted area is the site of the lesion, which is covered by a large scar; magnification, × 54.

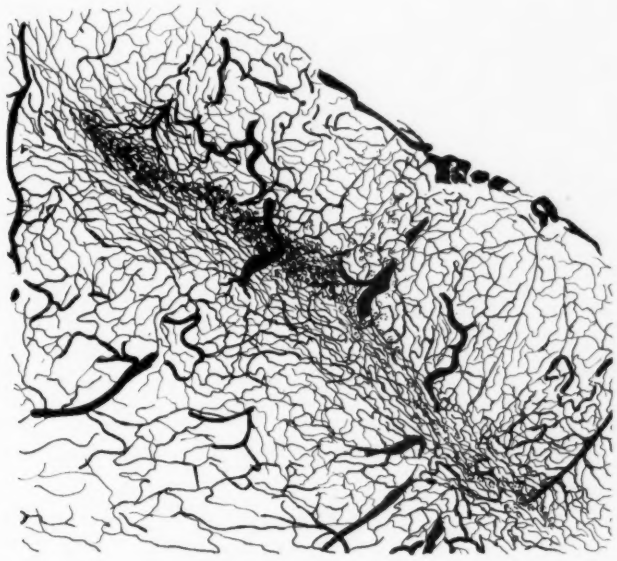

Fig. 4.—The capillary network in and around the undercut in rat 9b. The undercut is marked by scar tissues, the dotted areas in the figure; magnification, × 54.

of the area of cortical injury, where one often recognized the presence of scar tissue or degenerated cellular elements.

I shall analyze the data further with respect to the six conditions mentioned in a preceding section, which some writers have regarded as likely to affect the vascularity of tissues bordering a lesion.

Locality.—Topographically, the injuries inflicted to the neopallium in the experimental animals covered seven of the ten areas differentiated by Fortuyn.[7] The cortical fields spared were c, f' and k. In all probability the condition in the three areas would not be different from that in other fields, if there were injuries in them. Rats 2, 4 and 9 had lesions on both hemispheres. In most instances macroscopically and microscopically the parts adjoining a lesion were more vascular than other parts of the cortex, no matter in what topographic or functional areas the lesion was located and whether it was on one or both hemispheres.

Another point relevant to the question of locality is the position of the injury in relation to the large blood vessels. The outer surface of the rat's cortex is supplied mainly by the middle cerebral artery. Most of the lesions cut off one or more branches of this vessel. Only in rats 2b and 8 was the injury pretty far from the large branches. But the results showed that the high vascularity of the surrounding tissues was not in any way affected by their contiguity to, or remoteness from, the large vessels.

When a vascular trunk was interrupted by a lesion, the region formerly supplied by its terminals was still of normal vascularity. The interrupted terminals usually lost their old affiliation and entered into intimate relations with neighboring trunks. It was in such instances that an originally anastomosing capillary was more likely to enlarge its caliber and become an important communicating twig between two large branches. Thus, in the case of the rat at least, the results do not support the view of Campbell[8] and others that the interruption of a vascular trunk does incalculable damage to the region normally supplied by it as well as to other parts adjacent to, or even remote from, that region.

Size.—The size of the lesions varied widely in the experimental cases. The total area ranged from 1.5 to 10.3 per cent (in rats with injuries to both hemispheres I added together the separate lesions). The size of the lesion on one hemisphere varied from 0.4 to 6.2 per cent. Other things being equal, the larger the lesion the more feeding vessels cut off from the neighoring parts. This is especially true when these parts are situated at some marginal region, e. g., the occipital pole. In spite of the differences in the extent of the wounds, higher vascularity was found generally in cortical tissue adjoining large as well as small lesions.

Shape.—The experimental lesions were in different forms: horseshoe-shaped, roundish, S-shaped, pear-shaped, round, ring-shaped and rhomboid. Pains were taken to make a perfect ring-shaped lesion. The trephine was driven deep, and a perfect circle was described on the cerebral cortex. But the circumsected cortical mass was usually displaced by hernia of the hippocampus, owing probably to intracranial pressure. Consequently the lesion became round, instead of ring-shaped.

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7. Fortuyn, A. E. B. D.: On the Cell Laminations of the Cerebral Cortex in Some Rodents, Arch. Neurol. & Psychiat., Path. Lab. **6**:221, 1914.

8. Campbell, A. W.: Histological Studies on the Localisation of Cerebral Function, London, Cambridge University Press, 1905.

The only one approaching success was in rat 7. Since the neopallium derives its blood supply mainly from the large trunks on the outer surface of the brain, a perfect ring will cut off the chief vascular channels from the encircled mass. The only source of circulation, apart from the possibility of new blood vessels growing into this region, is through capillary anastomoses with other parts underneath the lesion. This should be a good test of the possibility of forming adequate vascular channels through a limited source of supply. A horseshoe-shaped lesion is also good for the same reason; an example was in rat 1. The enclosed cortical mass in both animals was profusely supplied with capillaries. Notwithstanding the different forms of the lesions, the results showed the same general tendency: The parts adjoining a cortical wound received a richer blood supply than usual.

Depth.—The deeper the wound, the less the chance for a cortical mass, especially when partially or completely encircled by injuries, to form vascular anastomoses with adjacent normal tissue in a particular direction. The ring-shaped and horseshoe-shaped lesions are good examples. There was, of course, a limit for the depth of a ring-shaped injury. When it reached the lateral wall of the lateral ventricle, the cylindric cortical mass would be completely isolated and perhaps absorbed later. In most animals the injuries involved all six layers of the cortex. Two wounds (rats 4a and 8) touched the superficial parts of the hippocampus. The undercut in rat 4b was largely in the corpus callosum, and that in rat 9b (fig. 4) was in the internal granular layer. The lesion in rat 2a (figs. 2 and 3) reached only the second layer at its deepest part. At certain levels of the injuries only the first, or zonal, layer was involved. It happened several times that mechanical pressure was the only effect registered, without any actual destruction of tissue. In short, the depth of the experimental lesions ranged from superficial mechanical pressure, through the six layers of the cortex, down to the hippocampus, yet the tissues surrounding the lesion generally showed rich vascularization.

Time.—The range of the interval between the operation and the injection was sufficiently wide, from ten to ninety-five days. In fact, an effort was made to parallel this study with the psychologic investigations of the effects of lesions of the brain, especially those performed in the University of Chicago laboratory. Before a psychologic test is given the animal is usually allowed from ten to fourteen days for recovery from the operation. For a long study the animal is kept in the laboratory for two or even three months. Intervals of from ten to ninety-five days should be sufficient to afford insight into the trophic condition of the cortical tissues surrounding a lesion during the whole career of the animal as a psychologic subject.

Theoretically, the vigorous repairing process immediately following an injury may cause an increase of blood supply to the adjoining tissues, and the enriched supply may soon subside. On the other hand, Buytendijk contended that the circulatory disturbance is serious at first but may be restored later. As to the time factor, my results are positive; it has little to do with the vascular or trophic condition of the tissues surrounding a lesion. The surrounding regions generally showed increased vascularity, no matter whether the injection into the brain was made ten or ninety-five days after operation (compare the camera tracings of rat 2a and 9b, figs. 3 and 4).

Kind of Operation.—Three types of instrument were used for the operations: trephine, needle and electric thermocautery. One may consider the wounds caused by the first two types of instrument as wounds resulting from mechanical destruction, while those caused by the third type are wounds from mechanical destruction

as well as from burning. I should mention also the effects of mere pressure. Macroscopically and microscopically there was no substantial difference between the effects of injuries produced by mechanical destruction (rat 2b, fig. 2, and rat 9b, fig. 4) and those of injuries caused by the combined form of destruction and heat (rat 2a, fig. 2 and 3, and rat 3, fig. 2). The adjoining parts were generally more vascular than other regions. This was even true following mechanical pressure without actual loss of tissue. Contrary to Buytendijk's contention, heat produced no more thrombosis than mechanical destruction.

SUMMARY AND CONCLUSIONS

The vascular condition of the tissue adjoining a cortical lesion has been studied in nine rats by means of the injection technic, with the following results:

The vascularity of such regions was apparently increased. This was evidenced by one or more of the following changes: a greater number of blood vessels, a larger diameter of the feeding vessels and richer capillary anastomoses. This was true irrespective of the topographic or functional locality of the lesion, its size, its shape, the depth reached, the length of time from operation to injection and the manner of inflicting the injury.

The increased vascularity of the adjoining tissues assures their adequate nutrition.

Histologic changes alone of the nerve elements near the wound constitute a safe guide for determining the extent of the lesion.

There is an increase of vascularity in the tissue adjoining a central lesion; thus, such a region is assured normal or supernormal nutrition.

STUDIES IN MULTIPLE SCLEROSIS

VII. SIMILARITIES BETWEEN SOME FORMS OF "ENCEPHALOMYELITIS" AND MULTIPLE SCLEROSIS

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The suggestion that multiple sclerosis represents a late stage of a process which is recognized in its acute stage as acute "myelitis" or "encephalomyelitis" of certain types dates well back into the last century.[1] The scene of battle has changed somewhat and now centers less about the question whether the lesions of multiple sclerosis are progressive—it appears to be almost universally accepted that they are—than about the more specific point as to whether the disseminated foci of degeneration seen in the group of "demyelinating encephalomyelitides" or encephalomyelopathies most definitely represented by the postvaccinal and postmeasles forms represent an acute form of typical sclerotic plaques. The issue is a difficult one in itself, for it consists in attempting to compare an acute lesion with a chronic one. This difficulty is increased by the fact that several varieties of lesions may often be observed in each case of the same disease. The subject has been further beclouded because the etiology of both groups is still the subject of warm discussion; and certain hypotheses, such as that of the existence of a special group of ectodermotropic viruses, have been injected into it. It appears worth while, therefore, to reexamine the question on a purely descriptive basis, taking into account the case reports already published, the recent experimental data and the results of a study of a group of pathologic specimens examined in this laboratory with a view to settling some of the controversial points.

CONSIDERATIONS A PRIORI

If one admits that multiple sclerosis is a disease with an evolution one should be able to reconstruct a picture of what the first stages are

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The expenses of this investigation were defrayed by the Multiple Sclerosis Fund of Harvard University.

From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

1. von Leyden, E., and Goldscheider: Die Erkrankungen des Rückenmarkes und der Medulla oblongata, in Nothnagel, H.: Specielle Pathologie und Therapie, Wien, A. Hölder, 1897, vol. 10.

like. Since areas of loss of myelin occur with little gliosis and since no intense gliosis is observed without a loss of myelin, it seems probable that degeneration of myelin is an early step in the formation of a sclerotic plaque. The myelin is doubtless phagocytosed. In many plaques the axis-cylinders are degenerated. When any such intense destruction occurs, infiltration with lymphocytes is likely to result. Small lesions, even old ones, are usually perivascular. The description corresponds closely to what is observed in "encephalomyelitis" (fig. 1).

To trace the process in the opposite direction—myelin, once it is degenerated, is not reformed in the central nervous system of adults,[2] lymphocytes and phagocytes disappear in the course of time from areas

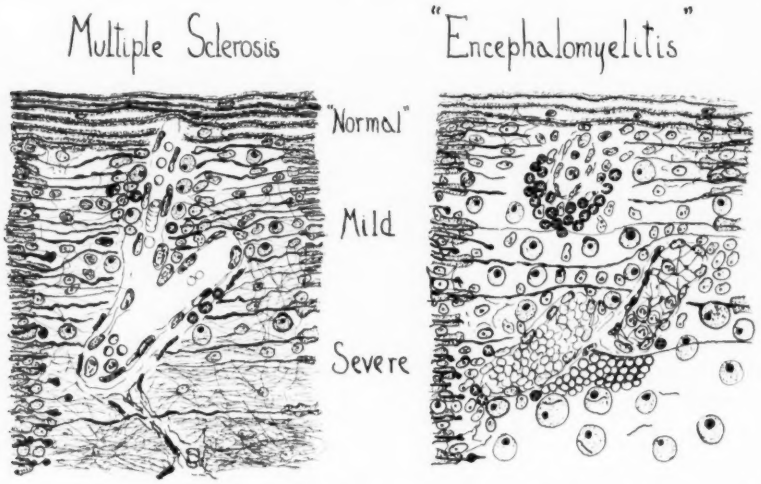

Fig. 1.—Diagram of the histology of a typical lesion of multiple sclerosis (left) compared with that of a typical lesion of "disseminated encephalomyelitis" (right). In both instances myelin (stippled) is lost. Axis-cylinders (heavy black lines) are damaged in both diseases but more so in "encephalomyelitis." Glial nuclei (oval, irregular, single nucleolus and fine chromatin) are increased in both, more perhaps in "encephalomyelitis," in which many show hyperstainability of the cytoplasm which may even appear ameboid. In multiple sclerosis a network of fine glial fibers has been laid down in older areas. Gitter cells (large cells with small round nuclei) carrying products of breakdown appear wherever myelin destruction is intense. Lymphocytes (dark, round, castellated nuclei) appear rarely in multiple sclerosis but frequently in "encephalomyelitis." Congestion and occasional extravasations of red cells are frequent in "encephalomyelitis."

of degeneration and injury to white matter leads to the formation of a glial scar containing connective tissue only if connective tissue is injured.

2. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931.

It is probable that the more gradually injury is produced, the larger the proportion of axis-cylinders which are spared; and a direct estimation shows less disparity between the lesions of "encephalomyelitis" and those of multiple sclerosis in this respect than has been generally supposed, as will be shown later.

ANAMNESTIC DATA

The situation would be far clearer if it were possible to obtain a history of the onset following measles or vaccinia—the two infections most frequently found to precede "disseminated encephalomyelitis"—in any large series of cases of definite multiple sclerosis, as it is possible to elicit a history of early syphilis in many cases of tabes. Although it is common enough to find that the first symptoms or later exacerbations of multiple sclerosis occur in association with acute infections of many varieties (in 4.2 per cent of five hundred and sixteen case reports collected by von Hoesslin [3]), measles and vaccinia are seldom mentioned among them; nor are there many instances in which patients suffering from postmeasles "encephalomyelitis" have survived long enough conceivably to permit the formation of gliotic lesions (a matter of months) and then have come to autopsy. I have been able to find reports of only three cases in the literature.

The case most satisfactorily described and best known is that of Walthard.[4]

> A 3 year old girl became stuporous, and choreic movements developed five days after the outbreak of a measles rash. On examination she was found to have paraplegia and signs of bronchopneumonia. She improved slightly but then lapsed again into coma. Convulsions developed, and she died four and a half weeks after the onset.
>
> Autopsy showed the presence of scattered foci of demyelinization, chiefly in the white matter of the hemispheres and brain stem. The outlines of these patches were irregular, and the author contrasted this with the sharp outlines of typical sclerotic plaques. The foci contained masses of fat-laden cells, and there was perivascular infiltration with phagocytic elements and lymphocytes. No plasma cells were seen. The axis-cylinders were largely destroyed, though in the illustrations they appear distinctly better preserved than the myelin. There were no cystic areas.

The author expressed the belief that the disease process was entirely different from that of multiple sclerosis, on the grounds that the myelin degeneration was diffuse and ill defined and there was such a widespread destruction of axis-cylinders. (Whether or not these are valid grounds for differentiation will be discussed later.) He stated that he was inclined to the belief that the condition more closely resembled diffuse

3. von Hoesslin, R.: Ueber multiple Sklerose: Exogene Aetiologie, Pathogenese und Verlauf, Munich, J. F. Lehmann, 1934, p. 101.

4. Walthard, K. M.: Spätstadium einer "Encephalitis" nach Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:176, 1930.

sclerosis. This seems entirely reasonable; but in some cases at least, of diffuse sclerosis, typical sclerotic plaques may be seen.

In the case just described the changes were only a few weeks old. From general pathologic experience it seems improbable that true sclerotic plaques could develop in so short a time. Particular interest attaches, therefore, to the less well known cases of Cramer [5] and of Schlesinger.[6]

In Cramer's case, that of a girl aged 19, paraplegia developed immediately after an attack of measles. The condition improved, and then the symptoms recurred. About a year after the onset psychic abnormalities were noticed. The patient became irritable, sleepless and suicidal and had to be confined in a hospital for patients with mental disease. No neurologic abnormalities were noticed. An abscess of the hip and a decubitus ulcer appeared. The patient died twenty-one months after the onset.

At autopsy irregular disseminated foci were observed. Microscopically the process was most marked in the neighborhood of vessels. In only one lesion was there complete absence of myelin; in others occasional sheaths could still be stained. Fat cells were numerous. These areas contained intact axis-cylinders. There were no areas of secondary degeneration. In some lesions in the cord the axis-cylinders were swollen and apparently degenerating.

Schlesinger's case, reported from Obersteiner's laboratory, was that of a boy aged 7 years. During the development of a measles rash he became extremely drowsy. After the acute disease was over he was extremely weak and was awkward in using his hands. Two or three weeks after the attack of measles he had headache, and his vision failed. The paresis of the limbs at first improved but then grew worse again.

On examination fourteen months after the onset the outstanding manifestations were atrophy of the optic nerve, an indefinite sensory loss and ataxia. There was incontinence of urine and feces. During the patient's stay in the hospital his speech became scanning, decubiti developed and there were signs of bronchitis. He died twenty-two months after the onset of symptoms.

Autopsy revealed the presence of numerous areas of myelin destruction in the cord, brain stem, cerebellum and hemispheres. The ganglion cells were little affected. The lesions involved gray and white matter indiscriminately.

Three types of lesions were distinguished. In one type all the normal nerve structures, except occasional axis-cylinders, were degenerated, and there was marked proliferation of glia and fat-laden cells. In another type the myelin was entirely destroyed, but the axis-cylinders were preserved. There was glial fibrosis but little phagocytosis of the products of myelin destruction. A third type consisted of areas in which the myelin stained only faintly—"shadow" plaques, such as have been frequently described in cases of multiple sclerosis.

Measles "encephalitis" was not recognized as an entity at the time of the publication of Cramer's and of Schlesinger's case reports, and the diagnosis was not made. The histories given are typical, however. In

5. Cramer, A.: Beginnende multiple Sklerose und akute Myelitis, Arch. f. Psychiat. **19**:667, 1888.

6. Schlesinger, H.: Zur Frage der akuten multiplen Sklerose und der Encephalomyelitis disseminata im Kindesalter, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **17**:410, 1909.

both cases the anatomic diagnosis of multiple sclerosis seems entirely justified by the description given.

The Outcome of Nonfatal "Encephalomyelitis."—It is sometimes stated that the postvaccinal and postmeasles nervous complications end either in death or in recovery.[7] This appears not to be an invariable rule, however. Persistent sequelae have been reported in a large number of cases by McAlpine,[8] by Stout and Karnosh[9] and by Ford.[10] They consist chiefly of hemiparesis, paraplegia, atrophy of the optic nerve and ataxia. In some instances late relapses and exacerbations have been reported.

An important point in this connection is that, while the "encephalomyelitides" which follow measles and vaccinia show a fairly constant pathologic picture post mortem, by far the larger number of examples of this same picture which have been reported have occurred without known infectious antecedents. The conditions have been classified as *neuromyélite optique,* disseminated encephalomyelitis and acute multiple sclerosis and under other names. In two of the three cases to be described in which the symptoms were acute there was no history of infection, yet the condition in these two cases closely resembled that in the third, which definitely followed vaccination. In some instances a similar pathologic process appears to be the result of a noninfectious agent. So with multiple sclerosis—the onset or exacerbations may seem to follow not only infection but an injury, pregnancy,[3] carbon monoxide poisoning[11] or some other exogenous cause, while in other instances no external factors may be found.

EXPERIMENTAL DATA

Lesions resembling those of "disseminated encephalomyelitis" were produced in a dog by Claude[12] by the injection of minute doses of tetanus toxin. Although he gave no illustrations of the foci, the description is sufficiently detailed to leave no doubt as to the nature of the process. Similar disseminated foci developed in an animal inoculated

7. Redlich, E.: Ueber ein gehäuftes Auftreten von Krankheitsfällen mit den Erscheinungen einer Encephalomyelitis disseminata, Monatschr. f. Psychiat. u. Neurol. **64**:152, 1927.

8. McAlpine, D.: Acute Disseminated Encephalomyelitis: Its Sequelae and Its Relationship to Disseminated Sclerosis, Lancet **1**:846, 1931.

9. Stout, R. E., and Karnosh, L. J.: Acute Disseminated Encephalomyelitis: Its Clinical Manifestations and Sequelae, J. A. M. A. **101**:667 (Aug. 26) 1933.

10. Ford, F. R.: Nervous Complications of Measles, with Summary of Literature and Publication of Twelve Additional Case Reports, Bull. Johns Hopkins Hosp. **43**:140, 1928.

11. Hilpert, P.: Kohlenoxydvergiftung und multiple Sklerose, Arch. f. Psychiat. **89**:117, 1929.

12. Claude, H.: Myélite expérimentale subaigüe par intoxication tétanique, Arch. de physiol. norm. et path. **29**:843, 1897.

with Aspergillus fumigatus by Ceni and Besta.[13] An excellent description is given, and some drawings are reproduced which also demonstrate that the lesions belong in the group under discussion.

Claude's work has been repeated and confirmed in this laboratory.[14] Among a large series of dogs inoculated with varying amounts of tetanus toxin, two presented a syndrome entirely similar to the one that Claude described. One of these animals died a month later, and microscopic preparations showed the presence of multiple disseminated foci, mostly perivascular, in which myelin was severely damaged or destroyed and in which proliferation of astrocytes and a perivascular infiltration sometimes with microglia and sometimes with lymphocytes occurred. The axis-cylinders were well preserved in most of these patches.

The second animal recovered from the acute lesions and was killed fifteen months later. Sections showed fewer areas of a similar type, except that there were less perivascular infiltration and a definite fibrous gliosis.

The lesions in the first animal corresponded closely, therefore, to the criteria usually accepted for "disseminated encephalomyelitis," namely, a perivascular distribution of myelin damage and infiltration with lymphocytes. In this instance the axis-cylinders were better preserved than in some cases in man. The lesions in the second animal were sclerotic plaques with practically intact axis-cylinders.

Further experiments in which demyelinization was produced by carbon monoxide poisoning and in which emboli of various types showed that it is a general rule that—at least in some experimental animals—the acute breakdown of myelin is followed at first by an exudate, sometimes gliogenous, sometimes hematogenous, and finally by gliosis.[2] The experiments most pertinent to the present discussion were those in which a venous obstruction was produced in the brain.[15] Under these circumstances there was in the majority of cases a diffuse glial proliferation in the affected white matter, the myelin underwent gradual degeneration and its place was taken by a dense astrocytic scar. In most lesions the axis-cylinders were practically unaffected.

A similar sequence of myelin breakdown, glial and lymphocytic infiltration and finally fibrous gliosis was produced by Ferraro[16] by means

13. Ceni, C., and Besta, C.: Sclerosi in placche sperimentale da tossici aspergillari, Riv. sper. di freniat. **31**:125, 1905.

14. Putnam, T. J.; McKenna, J. B., and Evans, J.: Experimental Multiple Sclerosis in Dogs from Injection of Tetanus Toxin, J. f. Psychol. u. Neurol. **44**:460, 1932.

15. Putnam, T. J.: Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935.

16. Ferraro, A.: Experimental Toxic Encephalomyelopathy, Psychiatric Quart. **7**:267, 1933.

of repeated injections of cyanide. In these experiments the axis-cylinders were relatively well preserved in some lesions but destroyed in others.

All these experiments have been criticized chiefly on the ground that the histologic pictures produced have differed in details from those of "encephalomyelitis," on the one hand, and multiple sclerosis, on the other. Occasion will be taken later to draw the experimental results also into the comparison between the two types of human disease.

MORPHOLOGIC COMPARISON OF MATERIAL FROM HUMAN SOURCES

In succeeding sections an attempt will be made to compare the acute disease with the chronic one, not case by case, but tissue by tissue, drawing as close an average as possible of the variations in each but also paying attention to the limits of variation. The data for comparison will be drawn largely from the literature. For multiple sclerosis the great source book is Dawson's monograph.[17] In addition, the works of Steiner,[18] Pette,[19] Hassin [20] and others will be referred to. For the disseminated encephalomyelopathies there is no single great source, unless it is Spatz' review.[21] Data derived from special studies in this laboratory of three cases of "disseminated encephalomyelitis" and fourteen cases of multiple sclerosis will be added.

Loss of myelin is a cardinal feature of the histologic picture of multiple sclerosis, particularly emphasized—perhaps even overemphasized—by the Weigert stain. Reconstructions show that smaller patches surround venules like a sleeve [22] (fig. 2). There is a certain tendency to symmetrical arrangement and to involvement of periventricular areas and the optic chiasm. The subcortical arcuate fibers are often spared.

So far, all observers are agreed. The older accounts, repeated in most textbooks, state that the lesions are entirely devoid of myelin, that they have rounded, clearly defined borders and that they are independent of the architecture of the tissues. While such lesions doubtless exist, being particularly common in the brain stem, and are tempting to photograph, variants are almost equally common elsewhere in the nervous

17. Dawson, J. W.: The Histology of Disseminated Sclerosis, Edinburgh, R. Grant & Son, 1916; Tr. Roy. Soc. Edinburgh (pt. 3) **50**:517, 1916.

18. Steiner, G.: Krankheitserreger und Gewebsbefund bei multipler Sklerose, Berlin, Julius Springer, 1931.

19. Pette, H.: Infektion und Nervensystem, Deutsche Ztschr. f. Nervenh. **110**:221, 1929.

20. Hassin, G. B.: Studies in the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:589 (May) 1922.

21. Spatz, H.: Die Anatomie der Psychosen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 7.

22. Falkiewicz, T.: Zur Pathogenese der multiplen Sklerose, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **28**:172, 1926.

system. They are best studied in the white matter of the hemispheres, where there is less chance of confusion between primary plaques and the results of secondary degeneration than in the cord. The use of thin sections and of the classic Weigert or Pal stain rather than the iron-mordanted variants will tend to increase the number observed. In almost any case areas may be observed in which the myelin is barely altered, being merely beaded or thinned ("shadow areas"); others, in which active breakdown is in progress and myelin or its fatty breakdown products are being phagocytosed in droplets; others, in which the phagocytic process has apparently subsided, leaving occasional distorted sheaths or none behind. Small areas of destruction of myelin are

Fig. 2.—Multiple sclerosis. An "early" plaque. Weigert stain.

almost invariably perivascular and round or oval. Large areas may be rounded but just as often are irregular or fade imperceptibly into comparatively normal tissue (fig. 5). "Islands" of preserved myelin may be left relatively intact in denuded areas, usually about venules. Occasionally bands of myelinated fibers mark off concentric areas of demyelinization—the "maplike" or "terraced" plaques. There appears to be no sharp line between multiple sclerosis and some forms of diffuse sclerosis.[23]

23. Wertham, F.: Small Foci of Demyelinization in the Cortex and Spinal Cord in Diffuse Sclerosis: Their Similarity to Those of Disseminated Sclerosis and Dementia Paralytica, Arch. Neurol. & Psychiat. **27**:1380 (June) 1932.

By definition the group of "encephalomyelitides" under discussion involves also demyelinization. In the cases of acute involvement, for example, most of the postmeasles and postvaccinal ones, the areas of demyelinization are numerous, small and perivascular. As in multiple sclerosis, the vicinity of the ventricle is a frequent site of plaques. In general, complete absence of myelin is the exception. The sheaths are thinned or beaded, or the myelin is being phagocytosed in droplets or as fat. Very close parallels may be observed, however, between such lesions and the smaller, obviously more acute plaques in multiple sclerosis (fig. 3). The irregular contour of larger, obviously confluent areas

Fig. 3.—Postvaccinal encephalitis. A small area of demyelinization is shown. Weigert stain.

may also be nearly duplicated in cases of multiple sclerosis of long standing. Rounded areas of loss of myelin have been described in instances of encephalopathy in which the clinical history as well as the paucity of acute "inflammatory" changes is evidence of a comparatively slow development.[24]

In the lesions produced in experimental animals, the early changes in the myelin were mild and breakdown of myelin was still in progress

24. Hassin, G. B., and Bassoe, P.: Multiple Degenerative Softening Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:613 (May) 1922.

at the end of ten months (fig. 4). Concentric areas of loss of myelin were observed by Ferraro in his dogs poisoned with cyanide.

Changes in the Axis-Cylinders.—Since the publication of Charcot's description it has been universally recognized that typical plaques of multiple sclerosis contain a large proportion of preserved axis-cylinders. The persistence of axons is such a cardinal point in the pathologic picture that many articles on the subject leave the impression that all are intact in all sclerotic plaques. This is certainly not the case, and modern pathologists who have made intensive studies of the disease (for example, Dawson, Spielmeyer, Jakob, Hassin and Bertrand) all agree that axons are seldom undamaged and are often completely destroyed and that secondary degeneration is common. Quantitative estimations of the proportion of fibers surviving are admittedly rare, for obvious reasons.

In the hope of obtaining some sort of an idea, however crude, of the degree of destruction of axis-cylinders, the available material was assembled from the laboratory collection which was prepared in such a way that the number of plaques per block could be counted and the plaques could then be divided into those in which axis-cylinders were substantially intact, those in which they were severely damaged and those from which they were practically absent. The estimates were necessarily somewhat arbitrary. The stains employed were either the ordinary Weigert and Bielschowsky types used on adjacent sections from the same block, or the Mallory or the Masson connective tissue stain on material fixed in formaldehyde, which gives an adequate differentiation of both myelin and axis-cylinders for the present purpose. Sections of the spinal cord were excluded on account of the confusion caused by secondary degeneration.

Thirty-five plaques from eleven subjects were studied. In four of them no definite diminution in the number of axis-cylinders could be observed on casual inspection. In thirteen plaques there was an unmistakable decrease in number, and in eighteen they were absent or the number was so far decreased that some high power fields were devoid of them.

In general, it appeared that smaller, acute plaques contained a larger proportion of axis-cylinders, while large plaques, especially those bordering on the ventricle, contained few (figs. 6 and 7). It is possible that a larger proportion of plaques containing preserved axis-cylinders would have been observed in specimens from the cord than in those from the hemispheres.

The available information in regard to the changes in the axis-cylinders in the acute "encephalomyelitides" is far less complete. It appears that there is an even wider range of variation than in multiple sclerosis. Areas may be seen, however, in which myelin appears irreparably damaged and yet the axis-cylinders seem merely spread apart by infiltration (fig. 8).

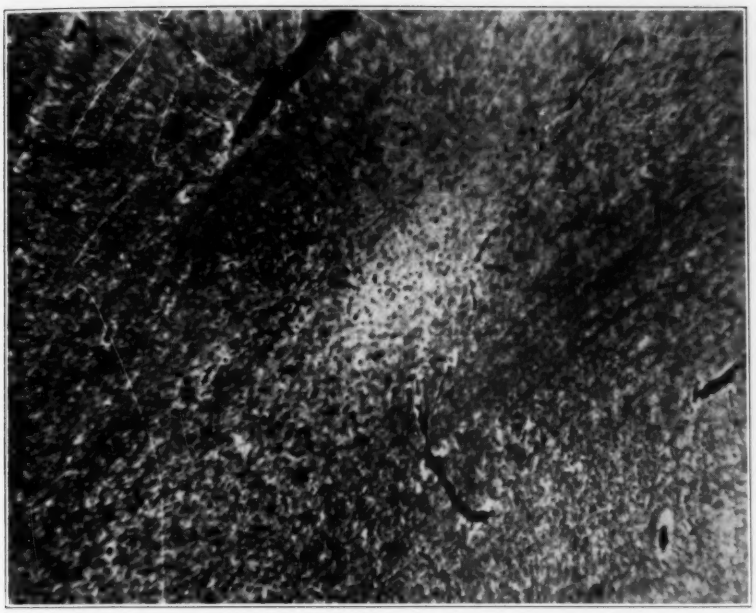

Fig. 4.—Experimental venous obstruction in a dog,[15] showing the loss of myelin thirteen months after operation.

Fig. 5.—Multiple sclerosis of several years' standing. Note the irregular diffuse loss of myelin in the two plaques near the ventricle. (Compare with figure 6.)

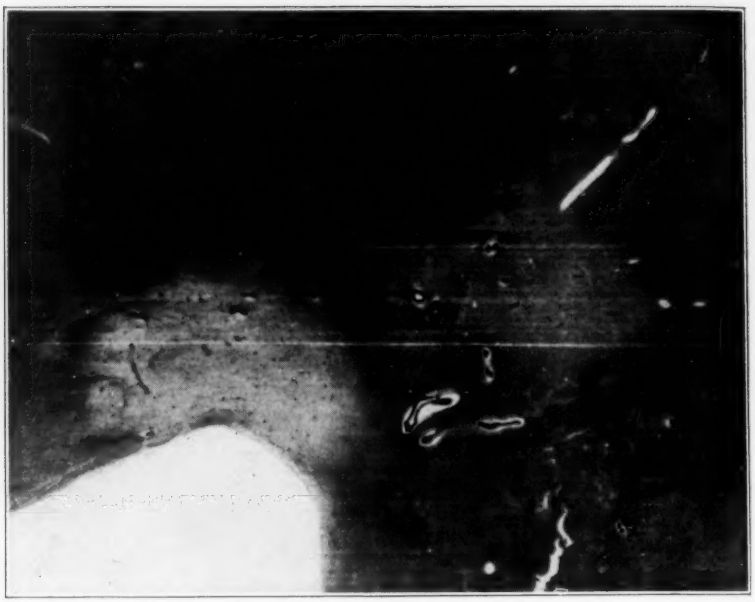

Fig. 6.—Multiple sclerosis. Section from the same block as that shown in figure 5 but stained by Davenport's method for axis-cylinders. Note that the loss of axis-cylinders almost parallels the loss of myelin in the plaque farther from the ventricle and that the axis-cylinders are entirely destroyed in the lesion bordering on the ventricle.

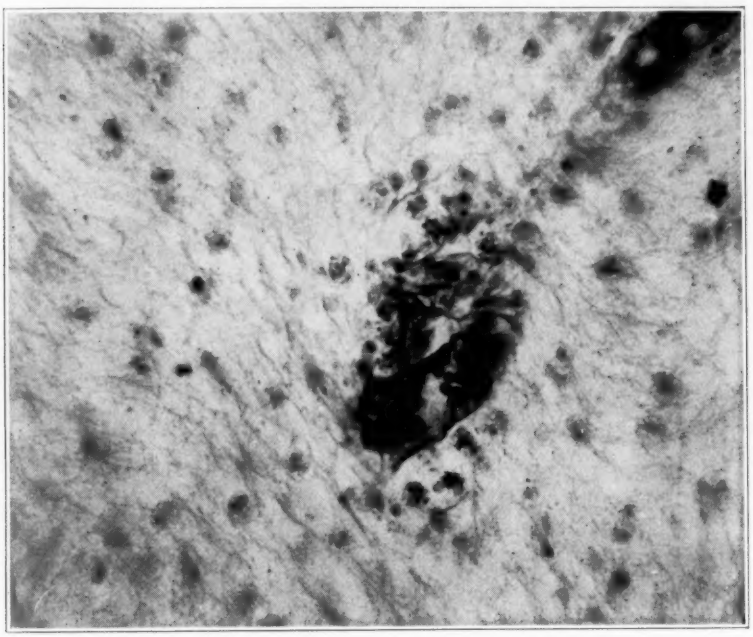

Fig. 7.—Enlargement of a portion of figure 6, to show the complete absence of axis-cylinders. The wavy gray lines are glia fibrils. The axis-cylinders are perfectly stained elsewhere in the section.

Fig. 8.—Postvaccinal encephalitis. Relative persistence of axis-cylinders in an area of loss of myelin.

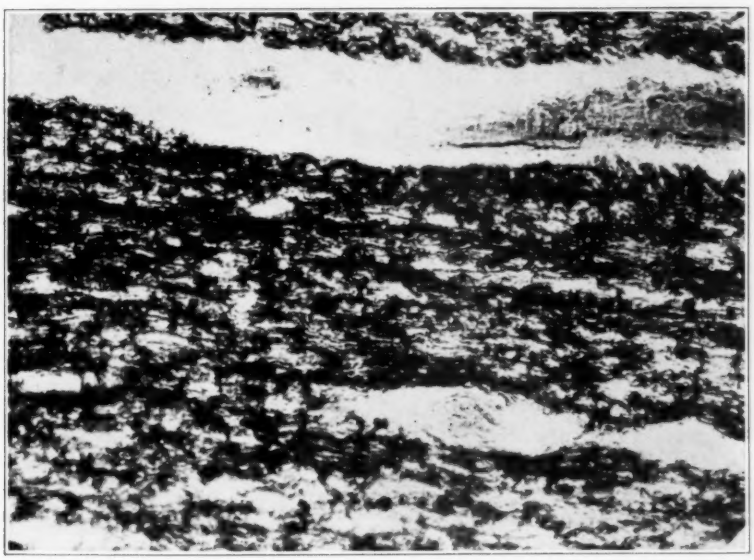

Fig. 9.—Practically complete preservation of the axis-cylinders in a completely demyelinated area ten months after experimental venous obstruction.[15]

The lesions produced in animals by the injection of tetanus toxin and by obstruction of venules have been characterized by the practically complete preservation of axons even in areas in which the myelin was completely destroyed (fig. 9). A parallel to the loss of axis-cylinders in the more severely damaged areas in multiple sclerosis and of "encephalomyelitis" is furnished, however, by certain forms of arterial embolism and carbon monoxide poisoning.[2]

Cellular Proliferation, Perivascular Infiltration and "Inflammatory" Phenomena.—The site of a collection of cells about a vessel in the central nervous system suggests the idea of an infection, despite the fact that recent investigations have shown that accumulations of lymphocytes and polymorphonuclear cells may occur under circumstances in which infection can be excluded.[25] Whether such phenomena should be called inflammatory or not is a problem which need not be dealt with here. It is probably wiser to confine the question to the single point as to how far the infiltrations observed in cases of multiple sclerosis correspond to those seen in cases of acute demyelinating diseases.

The fact that perivascular infiltrations occur in some (but not all) sclerotic plaques has been universally recognized since Charcot gave his description. It is generally admitted that the majority of the infiltrating cells are phagocytic and presumably microglial. Rod cells, another variant of the microglia, are occasionally seen in cases of multiple sclerosis. Proliferation of astrocytes, both diffusely throughout the tissue and in perivascular accumulations, is fairly constant. Acutely swollen "ameboid" astrocytes and even regressive glial changes are occasionally seen. There is often meningeal infiltration.

There has been some controversy as to the place occupied by lymphocytes. Most pathologists who have investigated the subject have reported seeing a few, and Symonds [26] has given convincing evidence that large accumulations may be seen. In some of the cases that were studied in this laboratory rings of cells of characteristic morphology were noted about vessels. There is a possibility that the round nuclei of fat-laden microglia may be mistaken for lymphocytes, but in one specimen from a patient who had had the disease for eighteen years appropriate stains for lipoids demonstrated that a perivascular collection of round castellated nuclei was not microglial. In the infiltration in one plaque even a few polymorphonuclear cells were observed.

25. Cone, W., and Barrera, S. E.: The Brain and the Cerebrospinal Fluid in Acute Aseptic Cerebral Embolism, Arch. Neurol. & Psychiat. **25**:523 (March) 1931. Yü-Lin, Ch'eng: Symptomatic Inflammation, ibid. **31**:1247 (June) 1934.

26. Symonds, C. P.: Pathological Anatomy of Disseminated Sclerosis. Brain **47**:36. 1924.

Microglial and astrocytic phagocytosis and progressive and regressive changes in the astrocytes are almost regularly described as occurring in the acute "encephalomyelitides." The diffuse glial infiltration even in the most active forms may closely resemble the fresher patches of multiple sclerosis. There is a variation from case to case in the relative degree of lymphocytic and glial infiltrations, respectively. An attempt has been made to divide the group into inflammatory and degenerative forms on this basis, but a survey of the literature and of the material in this laboratory makes such a distinction appear unjustified. As in multiple sclerosis, both types of infiltration may occur in the same case

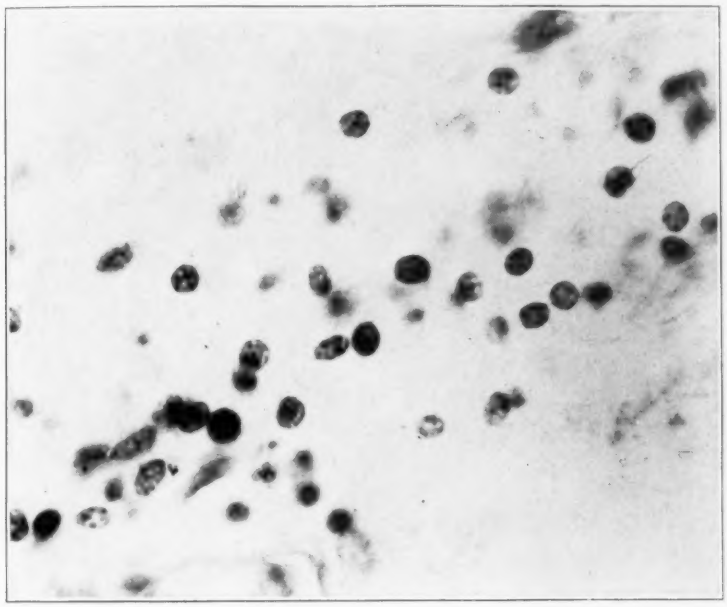

Fig. 10.—A group of cells, some of which have the morphology of lymphocytes. Appropriate staining of adjacent sections from the same block failed to show the presence of fat or myelin about the same vessel. Specimen from a patient with multiple sclerosis who had had symptoms for eighteen years. Iron hematoxylin stain of a frozen section.

(Spielmeyer [27] gives some striking examples), and either may occur in the relatively well defined postvaccinal and postmeasles forms.[28]

27. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930.

28. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles, Arch. Neurol. & Psychiat. **25**:748 (April) 1931. Globus, J. H.: Inflammatory Disease of the Central Nervous System: So-Called Nonsuppurative Encephalitis and Encephalomyelitis, ibid. **28**:810 (Oct.) 1932.

Lymphocytic infiltrations are doubtless more common in the "encephalomyelitides" than in multiple sclerosis and more common in the acute than in the older lesions of both groups.

All the glial reactions encountered in the acute "encephalomyelitides" were reproduced in the lesions resulting from venous obstruction in animals, including the formation of rod cells. Lymphocytic infiltrations were inconspicuous. Lymphocytes and plasma cells occurred in some of the lesions produced by tetanus toxin, but in others the response was exclusively glial. An interesting observation was made by Ferraro [16] in the areas of demyelinization produced by chronic cyanide poison-

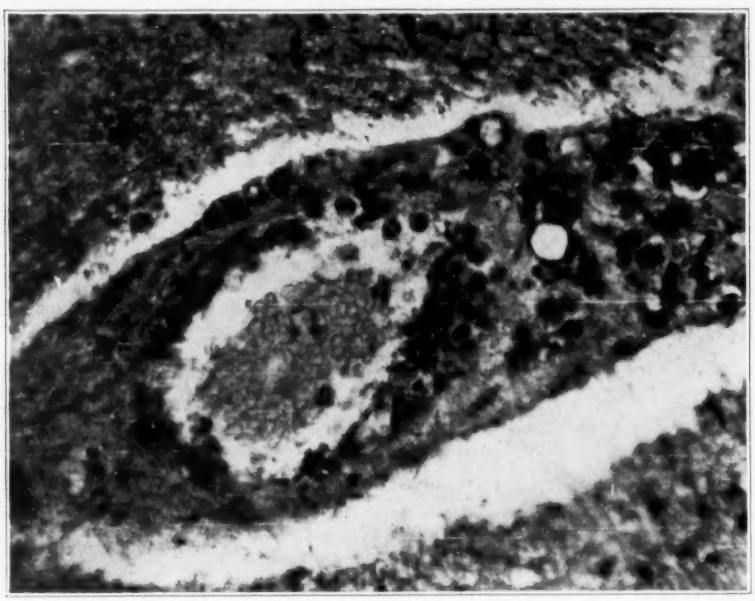

Fig. 11.—"Disseminated encephalomyelitis." Note the perivascular accumulation of yellow pigment and the mural thrombus. Masson's stain.

ing. In sixteen of these experiments a purely glial response was obtained; in two there were marked lymphocytic infiltrations.

Glial Fibrosis.—The glial scar is one of the most striking features of the lesions of multiple sclerosis, and it is sometimes stated that in no other disease does such a dense gliosis occur. This is probably incorrect. A careful comparison of the densest plaques of multiple sclerosis with areas of intense secondary degeneration about cysts of softening of arteriosclerotic origin two or more years old showed that the gliosis was at least as heavy in the latter condition as in the former. Further, it was observed that many plaques show only a moderate glial fibrosis, especially those in the hemispheres. They appear even grossly

Fig. 12.—Multiple sclerosis. Note the perivascular accumulation of yellow pigment. Masson's stain.

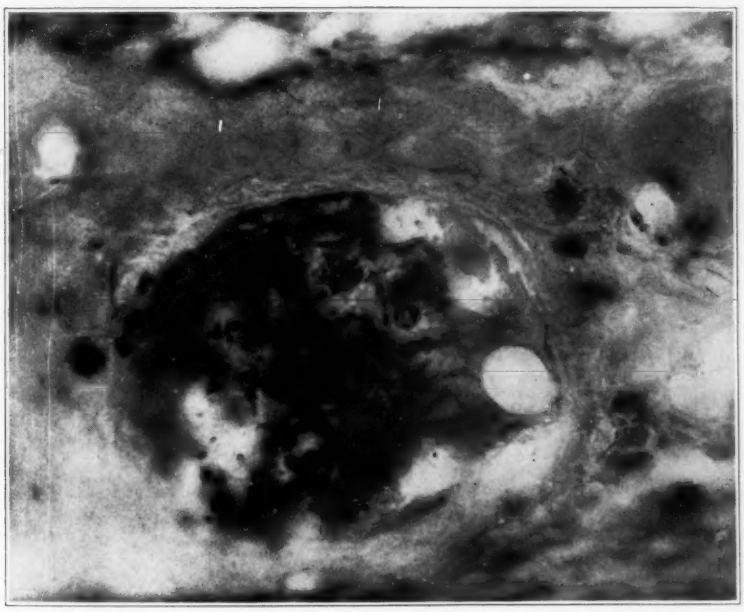

Fig. 13.—"Disseminated encephalomyelitis." There is shown a clot with fibrin, leukocytes and pigment within a vessel. Masson's stain.

Fig. 14.—Multiple sclerosis. There is a mass of débris and yellow pigment within a vessel. Masson's stain.

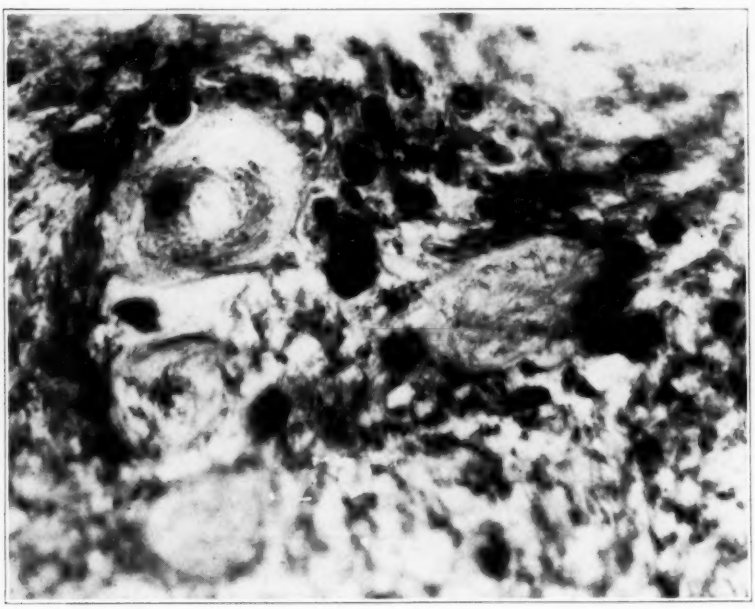

Fig. 15.—Multiple sclerosis. There is fibrous closure of a small vessel near the ventricle. Masson's stain.

as rarefied areas, softer than the surrounding tissues, and microscopically the glial network is filmy.

The gliosis is well known to be chiefly isomorphous; that is, the glia fibers are laid down parallel to the axis-cylinders. It seems as if the axons form a scaffold for the new fibers, as fibrin does for fibroblasts in tissue cultures. In certain plaques, however, the fibers radiate from blood vessels, and in these it is almost invariably observed that axis-cylinders as well as myelin have degenerated.

Glial fibrosis is, of course, absent in most cases of "encephalomyelitis" unless the patient has survived for several months, as in the cases reported by Cramer, Schlesinger and Walthard. There is frequently, however, a proliferation of astrocytes, which might be interpreted as the forerunner of gliosis. In Ferraro's animals and in the animals in this laboratory discernible gliosis began at about three months and was apparently still increasing at the end of fifteen months.

Vascular Changes.—Descriptions of the vascular changes in cases of multiple sclerosis and also of "encephalomyelitis" are usually limited to the adventitial infiltrations. The cells encountered have already been described. They need to lie for only a short period against the vessel wall before they become included by proliferation of the adventitial cells. This can be observed even in most cases of encephalitis of only a few days' duration.

More significant, perhaps, is the engorgement of vessels, which has been mentioned by practically all who have described the acute "encephalomyelitides" and is occasionally mentioned in regard to multiple sclerosis. In both groups of cases in the collection, dilatation and apparent proliferation of vessels are striking. In both diseases, but especially in the acute one, perivascular hemorrhages and deposits of pigments may occur (figs. 11 and 12). Clots are frequently observed in the vessel in association with the acute encephalitides [29] and rarely in association with multiple sclerosis,[30] but in the latter disease obliterated vessels are common (figs. 13 to 15). The vascular changes and their possible importance will be discussed more at length in another paper.

COMMENT AND SUMMARY

Sufficient data now appear to be available to settle the question of the relation of the acute disseminated "encephalomyelitides" to multiple sclerosis. Two cases have been reported in which a patient became ill for the first time with symptoms of cerebral involvement in the course of measles and passed through a course of remissions and exacerbations

29. Kreider, P.: Measles Encephalomyelopathy with Venous Thrombosis, to be published.

30. Putnam, T. J.: Material in preparation.

for several months and in which typical plaques of multiple sclerosis were noted at autopsy. Lesions closely resembling those of both diseases have been produced in animals by the use of tetanus toxin, by the experimental obstruction of cerebral venules and by chronic cyanide poisoning. All the histologic characteristics of "encephalomyelitis" may be seen in varying degrees in the more acute plaques of multiple sclerosis. The axis-cylinders may be preserved in the lesions of "encephalomyelitis" and may be destroyed in the plaques of multiple sclerosis. Glial fibrosis is the one distinguishing characteristic of multiple sclerosis, but it is not constant and is probably to be considered merely as evidence of chronicity. The structural differences between the two diseases can be explained as due to the intensity and duration of the diseases. Any consideration of the etiology of either the acute or the chronic disease should take into account the natural history.

Case Reports

GLIOMATOSIS OF THE LEPTOMENINGES

GEORGE S. MAHON, M.D., NASHVILLE, TENN.

Although the earlier literature contains many references to tumors of central nerve tissue characterized by local or extensive invasion of the leptomeninges, now known to be gliomas, methods for a more exact description and classification of such neoplasms based on the differential characteristics of the predominant cell have been employed only in relatively recent work. Originally, and even as late as 1924 and 1926, many of the cases of gliomatosis of the leptomeninges were reported as instances of sarcomatosis of the meninges. With the introduction of adequate staining methods, critical workers began to publish reports of new cases of this type and to restudy the old ones; it has been concluded [1] from the information thus acquired that practically all cases of leptomeningeal involvement by small-round-cell (sarcomatous) tumors are examples of gliomatosis, and true sarcomatosis of the meninges is extremely rare.

Before 1926 there had been reported fifty-six cases of sarcomatosis and twenty cases of gliomatosis of the leptomeninges. Detailed references, abstracts and comparative tables, including all these cases, are contained in the papers of Rach,[2] Jacob,[3] Ford and Firor [4] and Schuberth.[5] To these may be added sixteen subsequent cases of diffuse tumor of the meninges, reported by Cairns and Russell,[6] Connor and Cushing,[1b] Bailey and Cushing,[1a] Bailey [1c] (cases 1 and 2), Fried,[1d] Fro-

From the Department of Pathology of the Vanderbilt University Medical School.

1.(*a*) Bailey, P., and Cushing, H.: Medulloblastoma Cerebelli, Arch. Neurol. & Psychiat. **14**:192 (Aug.) 1925. (*b*) Connor, C. L., and Cushing, Harvey: Diffuse Gliomas of the Leptomeninges, Arch. Path. **3**:374 (March) 1927. (*c*) Bailey, Percival: Intracranial Sarcomatous Tumors of Leptomeningeal Origin, Arch. Surg. **18**:1359 (April) 1929. (*d*) Fried, B. M.: Sarcomatosis of the Brain, Arch. Neurol. & Psychiat. **15**:205 (Feb.) 1926.

2. Rach: Ztschr. f. Heilk. (supp.) **28**:78, 1907.

3. Jacob, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:249, 1910.

4. Ford, Frank R., and Firor, W. M.: Primary Sarcomatosis of the Meninges, Bull. Johns Hopkins Hosp. **35**:65 (March) 1924; Gliomatosis of the Meninges, ibid. **35**:108 (April) 1924.

5. Schuberth: Diffuse Sarcomatosis and Gliomatosis in the Meninges of the Central Nervous System, Deutsche Ztschr. f. Nervenh. **93**:34, 1926.

6. Cairns, Hugh, and Russell, Dorothy: Intracranial and Spinal Metastases in Gliomas of the Brain, Brain **54**:377 (Dec.) 1931.

ment, Dechaume and Christy [7] and Marchand and Picard,[8] making up to date ninety-two reported cases of diffuse tumor of the leptomeninges classified as either sarcomatosis or gliomatosis. According to Connor and Cushing, the cases of Cassirer and Lewy (case 1) and Markus, and possibly also those of Schaede (case 1) and Nonne, may be accepted as instances of true sarcomatosis in the old literature. The more recent cases of Fried, Connor and Cushing (case 1), Marchand and Picard and Bailey (cases 1 and 2) have received study adequate to justify the classification of the condition as true sarcomatosis. Hence, of the ninety-two cases of diffuse meningeal tumor originally reported as instances of either sarcomatosis or gliomatosis, only nine may be accepted as cases of true sarcomatosis, while the remaining eighty-three may be accepted as cases of gliomatosis. There is no doubt as to the nature of the condition in the majority (seventy-one) of the eighty-three previously reported cases of leptomeningeal gliomatosis, for in these cases there were one or more large primary tumors in the cerebrum, cerebellum or spinal cord, and the leptomeningeal involvement could be easily recognized as a secondary extension to the leptomeninges. Even the histologic nature of the primary glioma in most of these seventy-one cases may be fairly accurately diagnosed today in spite of the meager descriptions available and the insufficient differential methods used in the original studies. However, there are twelve cases of diffuse leptomeningeal gliomatosis in which a gross primary tumor was lacking and in which, in contrast to the massive or nodular secondary extensions of a primary intracerebral neoplasm, the condition manifested itself in a diffuse milky thickening of the leptomeninges, grossly similar to chronic leptomeningitis; the diagnosis in these cases of gliomatosis was, with two exceptions to be mentioned, based on negative rather than on positive evidence. The case to be reported resembles these twelve cases and in addition presents some features not previously reported.

REPORT OF A CASE

R. H., a farmer aged 32, was admitted to the Vanderbilt University Hospital on Oct. 11, 1934. The history was obtained from the patient and his father. As a child the patient had had frequent sick headaches, but he had been free from them since the age of 10 years. He had always been of a remarkably cheerful disposition. There was no history of any nervous or mental disorder in the family. The patient had had an enlargement in the neck for fifteen years.

Two years before admission, he had a sudden attack of severe bitemporal and occipital headache associated with vomiting. Mild muscular tremors and twitchings of all extremities developed, which lasted about one hour. About a month later he had another attack, characterized by more marked tremors, irrational speech and visual hallucinations. At about this time he began to notice impairment of the sense of smell, but he never had any olfactory hallucinations. The convulsive seizures continued to occur during the next year, recurring at intervals of from three to four weeks, growing increasingly more severe and finally being attended by clonic convulsions of the extremities. The attacks were usually preceded by an aura which the patient described as a weak, dizzy feeling, with

7. Froment, J.; Dechaume, J., and Christy, H.: Meningeal Diffuse Tumors, Lyon méd. **145**:813 (June 22) 1930.

8. Marchand, L., and Picard, J.: Ann. d'anat. path. **6**:1122, 1929.

tingling sensations over the whole body. When an attack occurred consciousness was lost for a period of from thirty minutes to six hours, and the returning conscious state was usually attended by hallucinations and unintelligible speech lasting for two or three days. For several days after an attack there were tingling and numbness over the lower part of the face on both sides, but no change was noted in the patient's disposition or character in the intervals between attacks. About a year and a half before his admission to the hospital hearing became impaired in the right ear, and there developed vertigo, associated with unsteadiness of gait, with staggering to the left. No tinnitus was present. A year before his admission vision began to fail, and bilateral blindness gradually developed. At about that time there was a spontaneous remission in the headaches and convulsions, which lasted for three months. Nine months before his admission the attacks returned and began to recur more frequently. Three weeks before the present hospitalization the patient was admitted to a hospital for patients with mental disease, from which he was transferred to this institution.

Examination.—The patient was fairly well developed and well nourished; his temperature, pulse rate and respiratory rate were normal. He was well oriented and cooperative but gave evidences of visual hallucinations during the period of examination. Memory was fair, being better for remote than for recent events. His disposition was cheerful and his intellect fair. When he spoke, the words and syllables were often run together, and the meaning of words was often confused.

The neck was slightly stiff, and there was a soft diffuse enlargement of the thyroid. The blood pressure was 120 systolic and 82 diastolic. General physical examination otherwise gave essentially negative results.

There was complete bilateral anosmia. The patient was completely blind, and the pupils did not react. There was low degree choking of both disks with marked secondary atrophy of the optic nerves. The extra-ocular movements were normal, and there was no ptosis or nystagmus. Facial sensation and the corneal reflexes were normal, and the muscles of mastication were unimpaired. There was weakness of central type affecting the right side of the face. Hearing was apparently diminished in both ears, but the results of audiometric tests were unreliable. Otherwise the cranial nerves showed normal function. General sensation was normal. There was no weakness of the extremities and no spasticity or hypotonia. The deep reflexes were normal and equal. The response to plantar stimulation was normal, and there was no clonus. A slight ataxia of all four extremities was present, but it was equal on the two sides. The gait and station could not be observed.

Urinalysis and examination of the blood, including the Wassermann test and estimation of the nonprotein nitrogen, sugar and carbon dioxide content of the blood, gave normal results.

Roentgenograms of the skull showed extensive erosion of the dorsum sellae and prominent diploic markings in the frontal region on both sides.

With the patient under anesthesia induced by tri-bromethanol in amylene hydrate, supplemented by local anesthesia, a ventricular puncture was performed on the left side on October 16. The cerebrospinal fluid was under greatly increased tension. Eighty cubic centimeters was withdrawn and replaced by air. Ventriculograms showed a marked dilatation of both lateral ventricles and of the third ventricle, without deformity or displacement.

Course.—Immediately after ventriculography the ventricle was again tapped, and the excess air and a considerable amount of fluid were evacuated. Examina-

tion of the fluid showed 200 white blood cells per cubic millimeter. One observer reported seeing a few gram-positive diplococci; however, this observation was not confirmed. After ventriculography the right pupil reacted to light, contracting to the size of a pinpoint.

The patient was somewhat drowsy, but his condition was otherwise satisfactory until 5 a. m. on the following morning. At that time the blood pressure rose rapidly to 240 mm. of mercury; the pulse rate and respiratory rate became slow, and the patient could not be aroused. Ventricular puncture, with removal of 110 cc. of fluid, gave temporary relief, but the patient did not rally; acute pulmonary edema developed, and he died at 9:40 a. m.

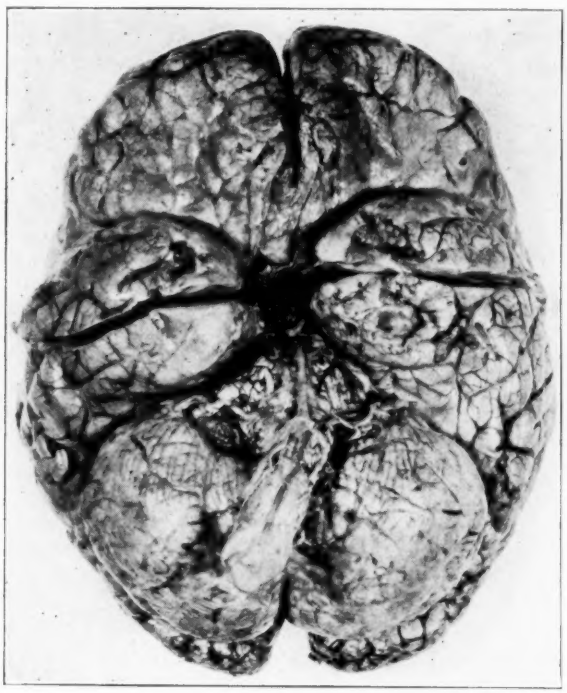

Fig. 1.—Brain showing leptomeningeal changes.

Necropsy.—Examination was performed two and one-half hours after death. The lungs showed a few healed, calcified tubercles. Except for that, routine gross and microscopic examination of the viscera gave negative results.

The dura was tense and bulging, and many large cerebral herniations presented externally along the superior sagittal sinus anteriorly and over the great wings of the sphenoids. The herniations had eroded the great wing of the left sphenoid. The bony floors of the anterior and middle fossae of the cranial cavity were of tissue-paper thinness.

The brain weighed 1,740 Gm. The convolutions appeared markedly flattened. The leptomeninges over the entire cerebrum showed slight thickening and had a milky, yellowish-white appearance, suggesting a chronic proliferative meningitis (fig. 1). Palpation revealed the affected areas to be definitely indurated rather

than softened, as would be expected had a purulent process been present. This process of thickening of the leptomeninges was most evident over the olfactory bulbs, over the whole inferior surface of the frontal lobes, in both sylvian fissures, extending well up onto the lateral convexities of the hemispheres, and over the cerebellum, especially over the vermis and the inferior surfaces of the lateral lobes. In the aforementioned regions the meningeal thickening was often sufficiently marked to obscure the sulci and gyri; this was best seen over the cerebellum, where the milky white thickening of the meninges involved irregular areas of considerable extent, overlying and completely obscuring the cerebellar surface markings. Even over the superior convexities of the hemispheres there was some evident milky cloudiness of the meninges, though it was not so pronounced as in the areas first listed. In the latter areas (over the convexities) the thickening and cloudiness became most evident along the lines of the sulci after

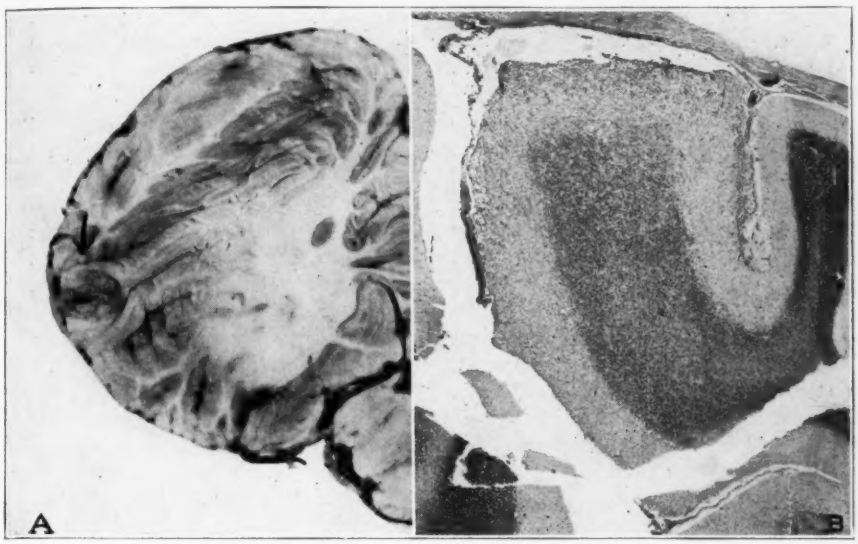

Fig. 2.—*A*, gross cerebellar nodule (natural size); *B*, microscopic cerebellar nodule (× 13).

fixation of the brain in a 10 per cent solution of formaldehyde. No circumscribed masses of tumor tissue were evident on the exterior of the medulla, pons, base of the brain, cerebellum or cerebral hemispheres; there was no evident block at the fourth ventricle. Only the part of the cord which could be removed through the foramen magnum was obtained.

On section, the leptomeninges were seen to be thickened everywhere; in many sections, such as at the tips of the frontal lobes, the cerebellum and the sylvian fissures, the thickening amounted to as much as 1 mm. In the cortex of the right lateral border of the cerebellum was a pear-shaped tumor, 1 cm. in diameter, sharply defined and composed of firm white tissue (fig. 2). After the tumor had been located by section, it was found to be evident externally as an elevation projection 2 or 3 mm. above the surface of the cerebellar lobe.

The ventricular system showed marked dilatation throughout. The cavity of the third ventricle was partially occluded by a thick layer of firm white tissue,

filling in the floor and the lateral portions of the wall, but the lumen was still patent. The ependyma of both lateral ventricles was remarkable by reason of many small white granulations, and the roof of the right lateral ventricle at about its midpoint (anteroposteriorly) showed beneath the ependyma a nodule, 1 cm. in diameter, projecting 2 or 3 mm. above the general surface and having a color darker than that of the surrounding ependyma.

Microscopic Examination: Sections were taken from the gross cerebellar nodule, the vermis, several areas of both cerebellar lobes, representative areas of the lateral and superior cerebral convexities, both optic tracts and olfactory bulbs and the underlying frontal lobes, the sylvian fissures, the tips of the temporal lobes, the upper part of the fourth ventricle, two different levels of the third ventricle, the lateral ventricles and the upper part of the cervical region of the cord. Paraffin sections were stained with hematoxylin and eosin and by Perdrau's method and also with the phosphotungstic acid-hematein and with Mallory's aniline blue stain, according to Davidoff's modification for formaldehyde-fixed tissue. Finally, representative sections were stained by the Pilcher-Owings method [9] for metallic impregnation of neuroglia cells in paraffin sections of formaldehyde-fixed tissues.

Under low power magnification the macroscopic nodule in the cerebellum had the appearance of a greatly swollen folium. It was richly cellular and showed no trace of the normal architecture of a folium. It displaced the adjacent folia laterally and infiltrated the contiguous molecular layers, while the deep portion underwent gradual transition from a tumor nodule to a normal folium. The impression could not be escaped that the nodule was actually the tip of a folium swollen to macroscopic size by a neoplastic process. The nuclei in the central portion were close together; those in the deep and superficial portions were rather widely separated. In the deep portion this separation was due to edema. In the superficial portion the loose structure was real, for the nuclei lay on the strands or in the interstices of a faintly acidophilic syncytial network. There were no areas of necrosis, but little lakes of edema were found even in the central and superficial portions, and necrotic cells (pyknotic nuclei, etc.) were scattered throughout the tumor. Mitotic figures were numerous; as many as from two to four could be seen in a single high power field. The tumor was richly supplied with blood vessels. In sections stained with hematoxylin and eosin the nuclei appeared of moderate though varying size. They were round, oval or even slightly elongated, were moderately dark owing to chromatin arranged in coarse granules and lacked nucleoli. No cytoplasm was seen in sections stained with hematoxylin and eosin except in the superficial portion, where it formed a loose syncytium, which was faintly acidophilic. But in sections stained with the phosphotungstic acid-hematein and with the Pilcher-Owings stain (fig. 3) many cells had a tadpole shape, due to a now evident long, tapering cytoplasmic process. Many of the cells had bipolar processes. The cells with round nuclei were surrounded by only a thin, ragged mantle of cytoplasm, without any processes. Rarely a cell was seen with a large vesicular, nucleolated nucleus surrounded by abundant well defined cytoplasm. These cells were thought to be neuroblasts. Coarse specifically staining neuroglia fibrils were abundant in the central portion of the nodule, and such fibrils were present but less abundant in the periphery (fig. 4). The only reticulum in the nodule was that in the walls of the blood vessels.

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9. Pilcher, C., and Owings, E.: A Stain for Neuroglia in Formaldehyde-Fixed Paraffin Sections, Arch. Neurol. & Psychiat. **35**:351 (Feb.) 1936.

In all sections from the cerebellum there were multiple foci of gliosis. These occurred on the surface of the folia and first became evident as an increase in the number of the larger neuroglia nuclei. There were many gradations of the process, and as the nuclei increased in number the folia became swollen. As the next step in the process the most superficial zone was observed to form a loose mass of cells histologically identical with those seen in the superficial part of the larger tumor or in the meningeal metastases. At several points this loose cellular mass extended among the fibers of the thickened overlying meninges. Frequently, just beneath the zone of Purkinje cells were seen areas of loose gliosis separating the molecular and the granular layer. One folium had, presumably by these changes, been converted into a microscopic nodule (fig. 2). The division into molecular and granular layers was still faintly discernible; mitoses were much

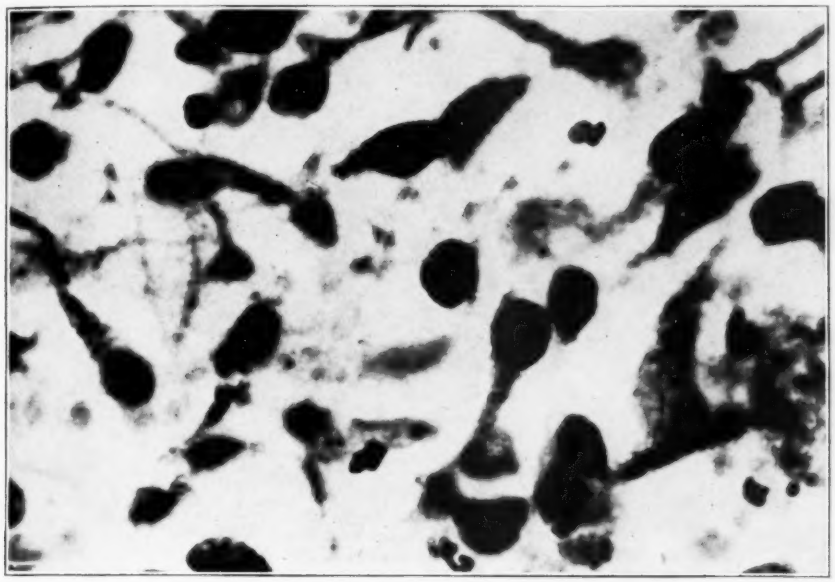

Fig. 3.—Central portion of the cerebellar nodule (Pilcher-Owings stain; × 1200). From Pilcher and Owings[9]; used by permission of the authors.

less frequent than in the gross nodule, and there was no invasion of the adjacent folia. There was no constant relationship between the gliosis of the folia and the degree of involvement of the overlying meninges.

The leptomeninges in all sections from the cerebrum, cerebellum and spinal cord were markedly thickened by collagenous tissue. The degree of thickening varied from point to point. It was most marked in sections from the cerebellum, sylvian fissures and inferior surfaces of the cerebrum, but there was no greater degree of involvement over the gross cerebellar nodule than was seen in several other regions. Over the superior and lateral cerebral convexities the collagenous thickening was extreme and compact. In some locations the thickening was slight over the gyrus but marked as it extended into the sulcus. Generally the fibrosis had fused the two layers of the leptomeninges, but vestiges of the subarachnoid space were still evident as smooth-walled spaces lying open in the deepest level of the thickened meninges.

Metastatic tumor cells were infrequent in sections from the cerebral convexities but were present in great numbers in sections from the cerebellum, sylvian fissures and inferior cerebral surfaces. The cells occurred as large, loose masses that lay in the subarachnoid spaces and were histologically identical with the cells in the superficial zone of the gross nodule. However, no mitotic figures or glia fibrils were present in these groups; the cells showed no polar processes, and no reticulin was demonstrable by Perdrau's method. Smaller groups of similar cells were scattered intimately through the meninges, lying within the interstices

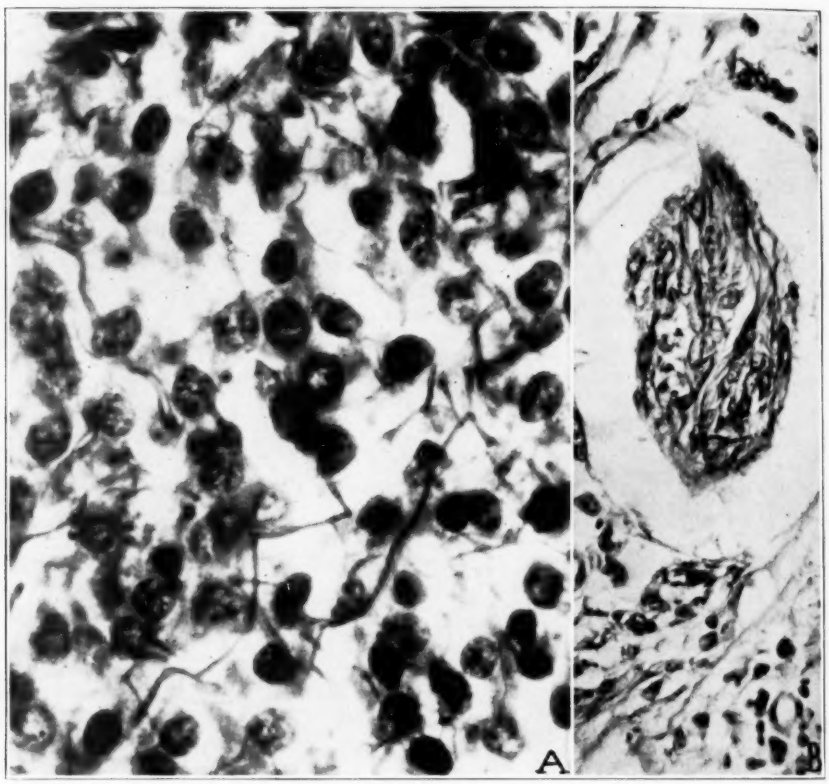

Fig. 4.—*A*, coarse intercellular fibrils in the center of the gross cerebellar nodule (phosphotungstic acid-hematein stain; × 900); *B*, bundle of polar spongioblasts in the subarachnoid space (phosphotungstic acid-hematein stain; × 375).

of the collagenous stroma. Perdrau's method demonstrated the absence of reticulin in these masses. The Pilcher-Owings stain demonstrated a unipolar process for an occasional one of these cells. A third type of group of metastatic cells occurred either in the subarachnoid space or among the collagen bundles of the meninges. The nuclei were elongated and closely applied to each other, forming bundles. The cytoplasm was finely fibrillated, and many coarse intercellular specifically staining neuroglia fibrils were seen. The whole group was so compact that only occasionally could a polar process be defined. No reticulin could be demonstrated among these cells. In spite of the intimate relation between many of these groups of cells and the collagenous stroma there seemed to be no doubt that the

cell groups were not fibrous tissue elements but represented invasive tumor cells that had infiltrated the meninges and differentiated to the point of acquiring polar processes and both intracellular and extracellular fibrils.

There was nowhere any retrograde perivascular infiltration or direct invasion of brain substance by tumor cells from the overlying meninges.

The tissue stenosing the third ventricle consisted entirely of dense fibrous gliosis. At several points the ependyma had ruptured and there lay partially detached into the ventricular lumen masses of cells histologically indistinguishable from the first type, described as lying within the subarachnoid spaces. The granulation over the walls of the lateral ventricles had a similar composition.

COMMENT

The type of tumor described is unusual. The individual cells, both in the macroscopic nodules and in the meninges, were morphologically either medulloblasts or spongioblasts. Yet the tumor tissue as a whole was not characteristic of medulloblastoma, glioblastoma multiforme or spongioblastoma polare and could not be fitted into any of the usual schemes of classification. Many different interpretations can be put on the microscopic observations, and it appears impossible to state definitely the origin of the tumor.

According to one possible interpretation, the changes over the surface of the cerebellum seem to have the greatest significance, as the leptomeningeal process might be considered to have originated from the multiple foci over the surface of the cerebellum. The foci of moderate glial proliferation might be considered as the least advanced lesions, and as such benign, so to speak, and not yet contributing to extensions of the tumor growth in the leptomeninges. The merely thickened folia, the desquamating folia, the microscopic nodule and the gross tumor might be interpreted as increasingly advanced stages of a process which appeared spontaneously and almost simultaneously in multiple independent foci over the surface of the cerebellum. This interpretation makes it necessary to suppose that some foci underwent more rapid growth than others; that the proliferating cells in these foci became more undifferentiated in character and had a tendency to form increasingly malignant (i. e., invasive) neoplastic tissue; that, in consequence, the gross cerebellar nodule was not alone in having a malignant neoplastic nature and contributing by the invasiveness of its component cells to the leptomeningeal process, and that, given more time, there would have been several macroscopic tumor nodules in the cerebellum. An unavoidable objection to such an interpretation is that tumors of the brain have not been proved to change their histologic nature, and such a change must be hypothesized if this interpretation is to stand.

If the foregoing hypothesis is not accepted, it might be urged that the gross cerebellar nodule was after all the primary growth responsible for the leptomeningeal changes. But the evident and striking disproportion between the chronicity of the leptomeningeal process and the small size and rapidly growing character of the cerebellar nodule cannot be ignored and speaks against the priority of this cerebellar lesion; it has been noted also that the leptomeninges over the nodule showed no greater involvement than did the leptomeninges of several other areas.

The multiple lesions over the surface of the cerebellum cannot be explained as retrograde invasion of the tumor from the meninges,

because there was nowhere any perivascular infiltration of cells and nothing which can be interpreted as more direct invasion of the cerebellum. The possibility must be considered that the lesions resulted secondarily from irritation of the cerebellar surface by a chronic meningitis. In that event, however, one would expect to find the same process over the surface of the cerebrum, and such was not the case. Also, groups of cells histologically indistinguishable from those in the meninges were seen to be desquamated from the surface of many foci, though in greatest numbers from the surface of the gross tumor, and it is recognized that although a secondary irritation of the surface of the brain (as from a chronic leptomeningitis) causes gliosis in the underlying tissue, the proliferating cells are astrocytes, not the more undifferentiated types which were found in the cerebellar foci.

Another explanation for the origin of the leptomeningeal process may be found in the symmetrical growth partially filling the third ventricle. The proliferated subependymal tissue, like the cerebellar foci, evidently was contributing to the production of tumor cells which entered the stream of cerebrospinal fluid and then invaded the leptomeninges. It would be impossible to say with certainty, however, that the growth in the third ventricle antedated the cerebellar foci. The growth in the ventricle may have been equally responsible with the cerebellar foci for the production of the leptomeningeal process, but there is no evidence that it was alone the primary tumor growth. The true nature and significance of granular ependymitis in such cases remain to be determined. Nodules of proliferated subependymal glia are frequently reported to occur as concomitant changes in cases of gliomatosis of the leptomeninges, but it has been pointed out [10] that similar changes may be observed in such unrelated conditions as dementia paralytica and acute meningitis.

Two other possible explanations of the origin of the leptomeningeal process remain: 1. There may have been an undiscovered tumor of the brain or spinal cord. A tumor in the first location seems unlikely in view of the care with which the brain was examined. It cannot be stated that there was no tumor in the spinal cord, because the cord was not examined. But the lack of all clinical evidence of such a tumor makes its presence unlikely. 2. One might hypothesize, as did Froment, Dechaume and Cristy, that the leptomeningeal tumor arose from leptomeningioblasts that took on neuroglial characteristics. There is no evidence to support such a hypothesis.

Among the eighty-three cases of leptomeningeal gliomatosis reported in the literature, there have been found only twelve cases of diffuse gliomatosis of the meninges without a macroscopic primary tumor.[11]

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10. Wertham, Frederic, and Wertham, Florence: The Brain as an Organ, New York, The Macmillan Company, 1934.

11. Connor and Cushing.[1b] Schuberth [5] (case 1). Froment, Dechaume and Christy.[7] Coupland and Pasteur: Tr. Path. Soc. London **38**:26, 1887 (case 1). Schroder: Monatschr. f. Psychiat. u. Neurol. **6**:352, 1899. Cassirer and Lewy: Ztschr. f. d. ges. Neurol. u. Psychiat. **61**:119, 1920 (case 2). Bassoe, P., and Shields, C. L.: J. Nerv. & Ment. Dis. **44**:385, 1916. Kaiser, Hans: Diffuse Primary Sarcomatosis of the Leptomeninges, Beitr. z. path. Anat. u. z. allg. Path. **62**:265, 1916. Rach [2] (case 4). Jacob.[3] Redlich: Jahresb. f. Psychiat. u. Neurol. **26**:351, 1905. Hadden, W. B.: Tr. Path. Soc. London **36**:13, 1885.

A definite diagnosis of gliomatosis, based on adequate differential staining, has been made in only two of these twelve cases, the case of Connor and Cushing [1b] and that of Froment, Dechaume and Cristy.[7] The case of Connor and Cushing is unique in that the primary tumor was found in a microscopic nodule of medulloblastoma in a lateral recess of the fourth ventricle. One cannot know definitely the nature of the disorder in nine of the other cases, in which it was diagnosed variously as sarcomatosis, endothelioma, endothelial sarcoma, etc., and in the one of Schuberth, in which the condition was considered possibly infectious but more probably neoplastic, and it is chiefly on negative evidence that those cases are classified as instances of gliomatosis. I feel justified, then, in stating that in the literature to date there are found only two proved cases of diffuse leptomeningeal gliomatosis without a macroscopic primary tumor in the central nervous system. The case just reported may or may not be included with these two, according to the way one interprets the evidence. But it seems that the evidence is in favor of regarding it as a case of leptomeningeal gliomatosis without a gross primary tumor in the central nervous system.

SUMMARY

A case of diffuse gliomatosis of the meninges is described.

The tumor cells were relatively young and undifferentiated, being identifiable as medulloblasts and polar spongioblasts, varying in differentiation in different localities. The spongioblasts produced intercellular fibrils. Although the individual cells could be identified, the gross tumor was not characteristic of any of the recognized types of glioma.

The evidence in the case is not sufficient to explain the origin of the leptomeningeal process. It is suggested that the leptomeningeal tumor may have originated (1) in multiple foci diffuse over the cerebellar surface, the gross nodule being only the furthest advanced of these foci; (2) in the gross cerebellar nodule as a "primary" tumor growth; (3) in the growth in the floor of the third ventricle; (4) from an undiscovered primary tumor of the brain or spinal cord, or (5) from meningioblasts that took on neuroglial characteristics. Serious objections may be raised to each of these hypotheses.

It is suggested that this case may be added to the two cases previously reported in the literature in which gliomatosis of the meninges arose without a macroscopic primary tumor.

It is further suggested that every uncertain tumor of this general type should be studied with the understanding that it may be gliomatous, even though no primary tumor may be demonstrable grossly. The term "sarcomatosis of the meninges" should be discarded as a term to be loosely used to designate invasion of the leptomeninges by small round cells.

Clinical and Pathologic Notes

PUERPERAL ECLAMPSIA

A Neuropathologic Study

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The clinical picture of puerperal eclampsia undoubtedly suggests a severe toxic state. Such a view is amply confirmed by the histologic observations of the condition of the visceral organs—the liver and especially the kidneys. Reports of detailed histopathologic studies of the central nervous system are scarce. As Dr. R. H. Jaffé gave me the opportunity to make a study of five cases of puerperal eclampsia, I am reporting here briefly the results of my observations on the changes in the central nervous system.

REPORT OF CASES

Case 1.—*Multipara; eclampsia in labor; death seven hours after delivery. Edema and rarefaction of the brain; degenerative changes of ganglion cells; progressive (proliferative) reaction of the glia, blood vessels and meninges; increase in the microglia; glial nodule in medulla with mild perivascular infiltration.*

History.—A white woman aged 33 was admitted to the Cook County Hospital on June 15, 1933, in a stuporous condition and died the next day. Relatives stated that the patient had never had convulsions until recently. She was in the eighth month of her ninth pregnancy.

Examination.—On admission the patient was obese and well nourished. She was stuporous; respiration was stertorous, and there was a bloody froth at the mouth. The temperature was 100 F.; the pulse rate, 96, and the respiratory rate, 24. The blood pressure was 172 systolic and 118 diastolic. Both eyelids were slightly edematous. The pupils reacted to light. There was no rigidity of the neck. The heart and lungs were essentially normal. There was a slight pitting edema of the ankles. The fetal heart tones were not heard. The cervix was soft and dilated 1½ fingerbreadths. The urine contained albumin (4 plus) and many hyaline and granular casts.

Course.—The patient had five convulsions. A dead fetus was delivered. The patient remained comatose and died seven hours later. The clinical diagnosis was eclampsia in labor.

Summary of the Gross Postmortem Observations (Dr. R. H. Jaffé).—Examination disclosed eclamptic nephropathy with distinct thickening of the basement membrane of the glomerular tufts and slight proliferation and lipoid infiltration of the epithelium of the tufts; slight thickening of the wall of the afferent arterioles and moderate thickening of the intima of the interlobular and arciform arteries; moderate fatty degeneration of the tubular epithelium (weight of the kidney,

From the Division of Neuropathology (Dr. G. B. Hassin), the University of Illinois, College of Medicine.

490 Gm.); moderate fatty changes in the liver, with irregularly scattered focal areas of necrosis (weight of the liver, 2,840 Gm.); moderate hypertrophy of the heart (weight, 415 Gm.); focal bronchopneumonia of the lower lobes of both lungs, hyperplasia and softening of the spleen (weight, 260 Gm.) and a puerperal uterus.

The brain weighed 1,160 Gm. The leptomeninges were congested but showed no other gross changes.

Microscopic Postmortem Observations.—The brain substance was edematous and more or less rarefied. The most noteworthy changes were in the ganglion cells, which exhibited marked chromatolysis and in some areas (motor areas, cornu ammonis and medulla) were severely degenerated. Many of the ganglion cells, including their axons and dendrites, were swollen; their nuclei were often displaced, and the nuclear membranes were dimly outlined or borken up. Some ganglion cells were reticulated; others were shrunken or elongated or appeared as shadows and liquefied. Neuronophagia was marked. The oligodendrogliocytes were swollen and increased in number. The Hortega cells (microglia cells) were numerous, especially in the cornu ammonis and in the regions of the inferior olivary bodies. In the medulla there was a focus or a nodule which consisted of proliferated glia cells and microglia cells (fig. 1*A*). A few of the adjacent smaller vessels were infiltrated with plasma cells and lymphocytes (fig. 1*B*).

The blood vessels in general were more or less congested, and the Virchow-Robin spaces were dilated. The capillaries were prominent; their endothelial and adventitial layers were hypertrophied and proliferated. Newly formed capillaries were not uncommon. The pia-arachnoid was distended; its meshes were widely separated and contained many histiocytes, fibroblasts and mesothelial cells and a few lymphocytes, polyblasts and red blood cells. The pial vessels were hyperemic, and their walls were thickened and slightly hyperplastic. The stroma of the choroid plexus appeared thickened and hyperplastic. The blood vessels were congested; the tuft cells were swollen, granular and vacuolated, and their nuclei were frequently pyknotic.

CASE 2.—*Multipara; eclampsia with two previous pregnancies; death in coma in tenth pregnancy. Edema and rarefaction of brain; marked degeneration of ganglion cells; numerous minute foci of softening; degenerated foci and small hemorrhages in basal ganglia and pons; proliferative and regressive changes in glia; sclerosis of cerebral and meningeal blood vessels; marked proliferative reaction of smaller blood vessels and capillaries; reactive aseptic meningitis.*

History.—A Negress aged 33 was admitted to the Cook County Hospital on Oct. 17, 1933, in a comatose condition and died the next day. The patient had had ten pregnancies and several times had been delivered in the Cook County Hospital. The first admission was during the sixth pregnancy, which terminated in the seventh month in eclampsia. During the ninth pregnancy the patient had headaches for two months, followed by dizziness, blurring of vision, insomnia and swelling of the ankles, face and hands. These symptoms gradually increased in severity and were associated with occasional vomiting and hematuria. The blood pressure at that time was 262 systolic and 160 diastolic; the urine contained 4 plus albumin, red blood cells and a few granular casts. The Kahn test of the blood was negative. After induction of labor by bag a 7 month fetus was delivered. Seventeen months later the patient was readmitted, in her tenth pregnancy; she was in a state of coma, and she died the next day.

Examination.—The blood pressure was 240 systolic and 150 diastolic. The urine gave a 4 plus reaction for albumin and contained many red blood cells. Chemical analysis of the blood showed: urea nitrogen, 23 mg. per hundred cubic centimeters; uric acid, 5.5 mg., and sugar, 75 mg.

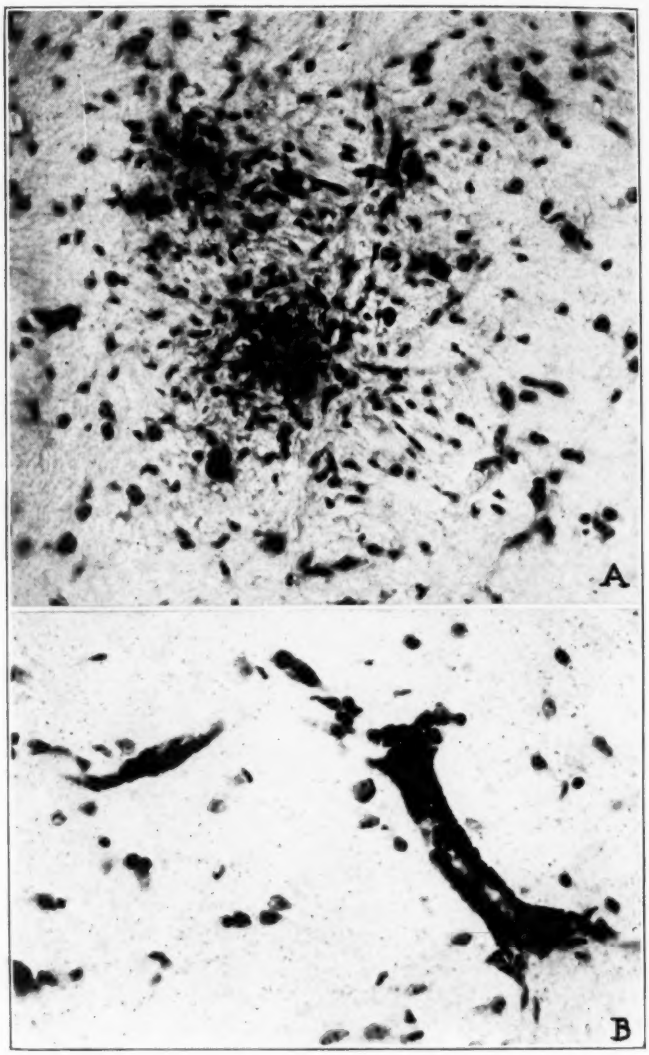

Fig. 1 (case 1).—*A*, a glial nodule in the medulla; *B*, perivascular lymphocytic infiltration of small blood vessels. Toluidine blue stain.

Course.—The course was afebrile. The patient had no convulsions and remained comatose until death. Because of the increase in the amount of uric acid in the blood the condition was regarded as eclampsia without convulsion.

Summary of the Gross Postmortem Observations (Dr. R. H. Jaffé).—Examination disclosed eclamptic nephropathy with distinct thickening of the basement membrane of the glomerular tufts and extreme bloody engorgement of some of the tufts; hyaline droplet degeneration of the capsular and tubular epithelium; moderate sclerosis of the arterioles (weight of the kidneys, 400 Gm.); edema of the liver, with focal subcapsular areas of extreme capillary congestion (weight, 1,660 Gm.); marked hypertrophy of the heart (weight, 550 Gm.); congestion of the spleen (weight, 250 Gm.); diffuse colloid goiter, and a puerperal uterus.

The brain weighed 1,340 Gm. The convolutions were flattened; the brain substance was soft and very moist (edema).

Microscopic Postmortem Observations.—The brain substance was markedly edematous and more rarefied than in case 1. The ganglion cells also were more diffusely and severely affected. In addition, there were present: (1) minute multiple foci of softening, (2) foci of degeneration and minute hemorrhages, (3) sclerosis and (4) proliferative changes in the small blood vessels and capillaries.

The changes in many of the ganglion cells were similar to those described in case 1. However, a larger number of the ganglion cells exhibited so-called ischemic changes—shrunken and triangular shaped cells with pale stained and homogeneous cytoplasm and dark pyknotic nuclei, while others showed perinuclear or complete liquefaction. Neuronophagia was marked. The glia cells showed an increase, mainly in the form of glia nuclei and satellitosis. Mitotic figures were frequent. The number of microglia cells also was increased, especially in the cornu ammonis, basal ganglia and pons. On the other hand, regressive changes of the glia were not uncommon (white matter and basal ganglia). The outline of the cytoplasm of the cells was irregular, and the nuclei exhibited marked pyknosis (ameboid glia) and karyolysis (broken-up nuclei).

The foci of softening were present mostly in the white matter and pons and consisted of compact collections of glia and microglia cells. Many were transformed into gitter cells. In the pons there were gitter cells within the perivascular spaces of the smaller vessels (fig. 2*A*). The walls of these vessels were thickened and appeared edematous.

The foci of degeneration and minute hemorrhages were scattered mainly in the basal ganglia. The foci of degeneration consisted of pale areas and contained severely degenerated ganglion cells (fig. 2*B*) and minute blood vessels. These vessels were greatly distended with blood, and the perivascular spaces were dilated and infiltrated with erythrocytes. The walls of these vessels appeared degenerated and stained poorly. The lumens of some blood vessels were occluded by leukocytes and cellular débris. Reactive glial phenomena within or around the foci were, as a rule, absent, except for a focus in the cortex of the motor area (fig. 3). The cells of this focus were glia and microglia (Hortega cells) and formed a distinct nodule. A small blood vessel, poorly outlined, lay within the focus, while the adjacent ganglion cells, including the Betz cells, were severely degenerated (fig. 4).

The hemorrhagic foci contained many granules of blood pigment, some of which were enclosed within histiocytes. Some foci appeared as rings around the smaller blood vessels, the adventitial spaces of which were infiltrated with red cells. No reactive phenomena of any kind were present.

The blood vessels showed two types of changes: The changes which were evidently of a chronic nature, namely, thickening and hyperplasia of the vessel walls (the media and the intima in some of the smaller cortical vessels appeared as a connective tissue band, and the lumens were occluded by an organized thrombus); the other changes consisted of proliferation of the endothelial and adventitial cells of the smaller blood vessels and capillaries, especially in the basal

ganglia, pons, medulla and cornu ammonis. Mitotic figures were frequent. A few of the blood vessels showed mild perivascular lymphocytic infiltration; newly formed capillaries were numerous.

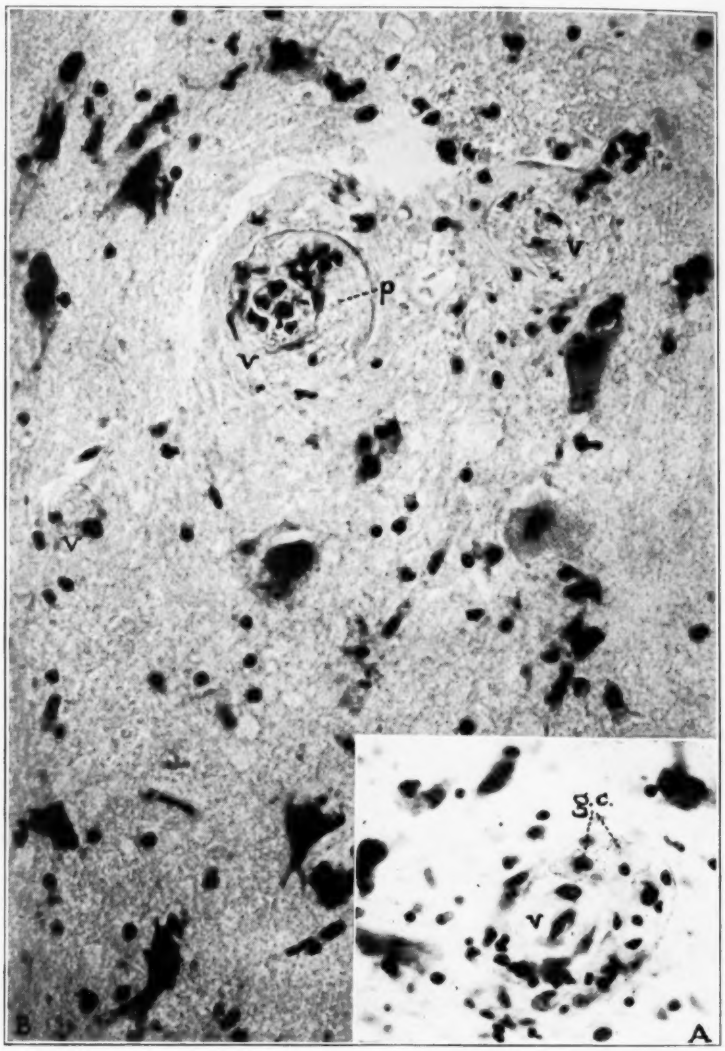

Fig. 2 (case 2).—*A*, a thickened small blood vessel (*v*) in the pons with a dilated perivascular space containing gitter cells (*g.c.*). Toluidine blue stain. *B*, a degenerated area in the optic thalamus, showing three small blood vessels (*v*), their perivascular spaces (*p*) filled with blood. Toluidine blue stain.

The pia-arachnoid was hyperplastic in some areas. In others the meshes were widely separated and contained many histiocytes, occasionally filled with blood pigment, fibroblasts, erythrocytes, mesothelial cells and some lymphocytes. Around

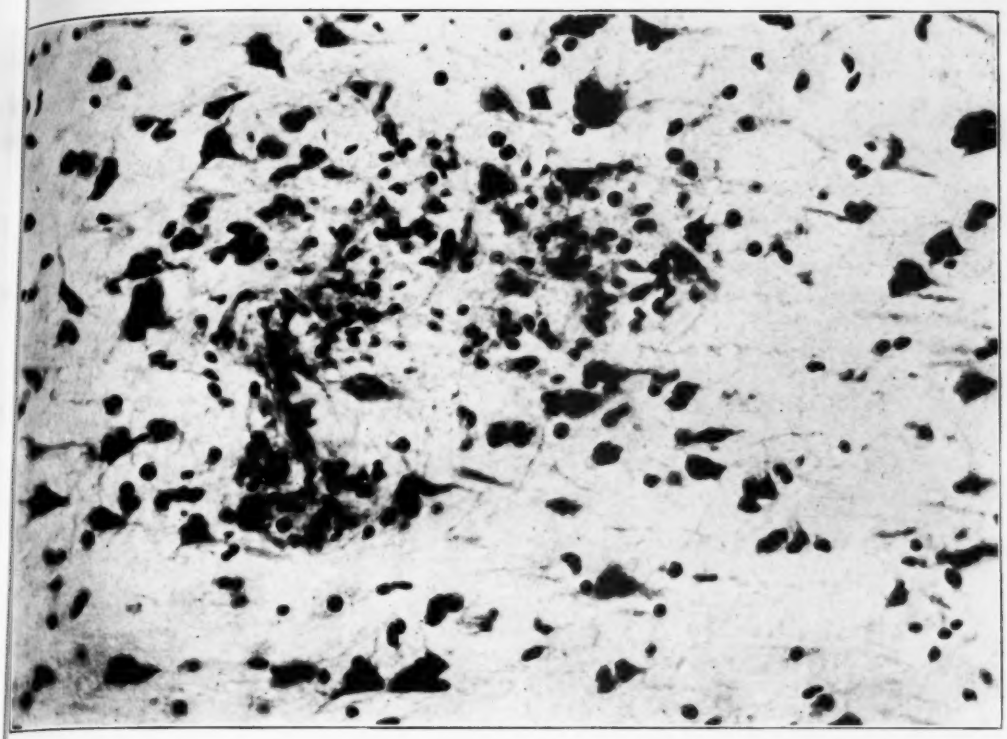

Fig. 3 (case 2).—A focus of degeneration in the motor cortex. Near the center of the focus is a blood vessel. The cell masses are proliferated glia and Hortega cells. Toluidine blue stain.

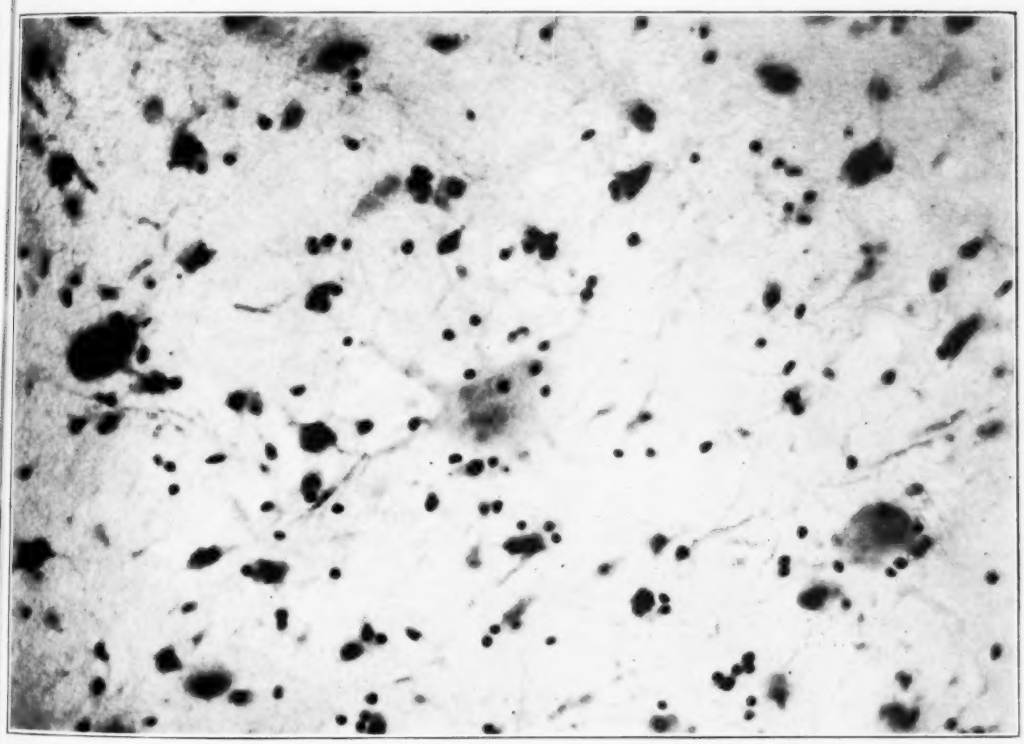

Fig. 4 (case 2).—Motor cortex. The large multipolar cells are severely degenerated Betz cells. Toluidine blue stain.

the cerebellum the meninges were hemorrhagic and contained many macrophages filled with blood pigment granules.

The vessels of the leptomeninges like those of the cerebrum, were hyperplastic, and some showed thickening of the intima. The smaller blood vessels also exhibited active proliferation of their walls and, like the larger blood vessels, were dilated and hyperemic.

The stroma of the choroid plexus was greatly thickened and contained many fibroblasts. The blood vessels also were congested, and their walls were thickened and hyperplastic. The tuft cells of the choroid plexus showed changes similar to those described in case 1.

CASE 3.—*Multipara; postpartum eclampsia; sepsis, convulsion, coma and death four days after delivery. Meningeal and cerebral hemorrhage (in left basal ganglia) with invasion of lateral ventricles; minute foci of softening (and degeneration) in pons and medulla; arteriosclerosis and plaques of calcification in basilar artery; cerebral edema and rarefaction of the nerve parenchyma; severe degenerative changes of ganglion cells; diffuse proliferation of glia, small blood vessels and capillaries; aseptic meningitis.*

History.—A white woman aged 28 was admitted to the Cook County Hospital on Feb. 5, 1924, in coma following what was apparently a normal delivery. A month previously she had begun to complain of general malaise and backache, followed by swelling of the ankles and diarrhea. Labor had been short and apparently normal. Soon after delivery the patient complained again of general malaise and backache and became nauseated. She vomited twice and then apparently fell asleep, breathing heavily. A few hours later she was found on the floor in a convulsion which lasted for two minutes. A previous pregnancy had been normal, and the past history was without significance.

Examination.—The temperature was 99 F.; the pulse rate, 54, and the respiratory rate, 24. The blood pressure was 132 systolic and 78 diastolic. The deep reflexes were exaggerated, and a Babinski sign was elicited bilaterally. The head was turned to the left and showed marked resistance when attempts were made to straighten it. The urine contained a good deal of albumin and many casts. The spinal fluid was blood tinged.

Course.—A diagnosis of postpartum eclampsia was made, but because the patient had fallen out of bed the possibility of a fracture of the skull also was considered. The blood pressure gradually rose, and the temperature reached 107 F. The patient died on Feb. 9, 1934, four days after admission to the hospital.

Summary of the Gross Postmortem Observations (Dr. R. H. Jaffé).—Examination disclosed massive hemorrhage in the region of the left basal ganglia, with invasion of the lateral ventricle; eclamptic nephropathy with distinct thickening of the basement membrane of the glomeular tufts and hyaline droplet degeneration of the capsular epithelium; dilatation of the afferent arterioles (weight of the kidneys, 340 Gm.); marked cloudy swelling of the liver (weight, 1,380 Gm.); infectious softening of the spleen (weight, 160 Gm.); suppurative endometritis, with retained degenerated placental tissue (cultures, hemolytic streptococci, staphylococci and atypical Bacillus Welchii).

Microscopic Postmortem Observations.—The white matter of the cerebrum and parts of the basal ganglia adjacent to the large hemorrhage were studded with numerous foci of extravasated blood cells and collections of gitter cells of varied sizes and shapes. Other foci appeared as rings around disrupted blood vessels.

The glia showed active proliferation, and many of the glia cells exhibited mitotic figures. The smaller blood vessels and capillaries in these areas were greatly hypertrophied and proliferated; their walls were often separated and infiltrated with erythrocytes, polymorphonuclears and broken-up nuclei (fig. 5*A*). Some blood vessels appeared disorganized, though both the endothelial and the adventitial layers showed active proliferation (fig. 5*B*), and mitotic figures were frequent. The proliferated adventitial cells often resembled fibroblasts; some appeared detached or lay free near the vessel wall. They were large, with long processes and large oval vesicular nuclei rich in chromatin granules. The ganglion cells in the deeper layers of the cortex—bordering on the white matter—were severely degen-

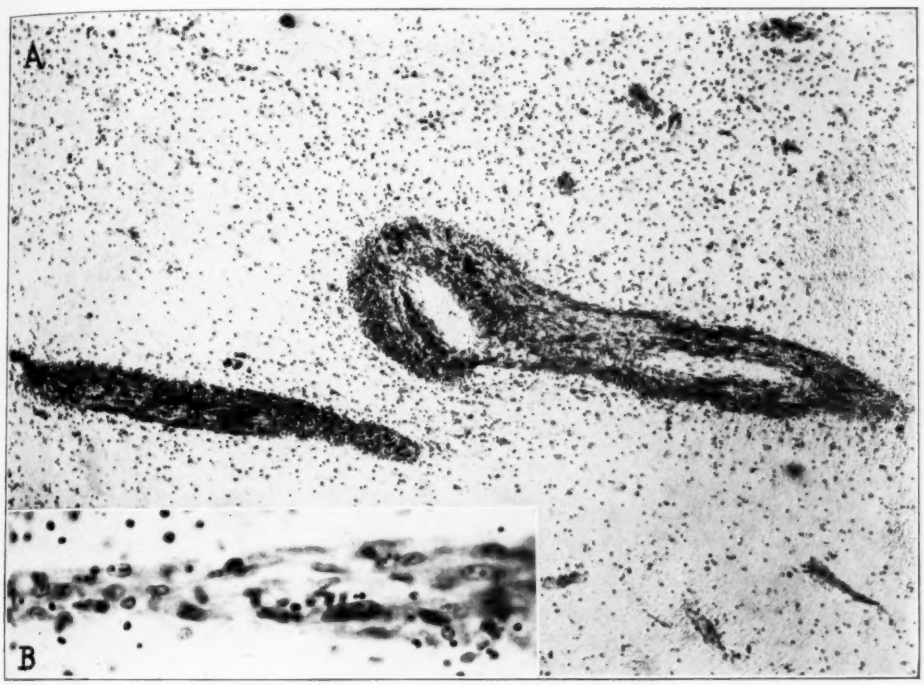

Fig. 5 (case 3).—Cerebral subcortex. *A*, foci of hemorrhages. The walls of the blood vessels are swollen and infiltrated with polymorphonuclears. *B*, hyperplastic adventitia. Toluidine blue stain.

erated and exhibited marked neuronophagia. In general the changes were similar to those described in the previous cases. Thus, the glia was diffusely proliferated, and mitotic figures were common in the glia cells. The microglia cells also were greatly increased in number; edema of the brain was marked, and the Virchow-Robin spaces were greatly dilated. Foci of softening and degenerated areas were present in the pons and medulla; they were very small and similar to those described in case 2. The smaller blood vessels and capillaries were congested throughout and moderately thickened, the endothelial and adventitial layers being proliferated. The capillaries were prominent; many were newly formed. The

basilar artery showed intimal thickenings; these were transformed into calicified plaques which protruded into the lumens of the blood vessels. The elastica in such areas was destroyed.

The pia-arachnoid was greatly distended by hemorrhagic extravasations. Within its meshes were a great number of macrophages (histiocytes), many containing blood pigment granules and red blood cells. As a whole the meninges were hyperplastic and contained, in addition to numerous histiocytes, fibroblasts, polyblasts, mesothelial cells, a few lymphocytes and polymorphonuclears. The pial vessels were much congested, and their walls were hypertrophied. The choroid plexus was hemorrhagic; the blood vessels were greatly congested. The stroma was thickened. There were many macrophages and blood pigment granules. The tuft cells were swollen and vacuolated.

CASE 4.—*Primipara; postpartum eclampsia nine days after delivery, with high temperature, delirium, rigidity of neck, vomiting, convulsions and death. Severe diffuse degenerative changes of ganglion cells; edema, rarefaction and proliferation of glia cells and capillaries; marked hyperemia of blood vessels; hemorrhagic extravasation into meninges over cerebellum; reactive aseptic meningitis and manifestations of so-called toxic encephalitis.*

History.—A Negress aged 17 entered the Cook County Hospital on May 9, 1934, and died on May 20, nine days after delivery. The postpartum course was uneventful until the ninth day, when the temperature rose to 105 F. and was accompanied with delirium. No further history was obtained.

Examination.—The patient was acutely ill. The temperature was 105 F.; the pulse rate, 120, and the respiration rate, 26. There was slight conjunctivitis; the heart was normal; the vagina was filled with foul pus. There was an episiotomy wound. There were 38,750 leukocytes per cubic millimeter of blood. The spinal fluid was clear and contained 90 cells. Cultures of the blood and spinal fluid proved to be sterile. The Pandy and Wassermann tests and those for gonococcic infection were negative.

Course.—The tentative diagnosis was puerperal sepsis. The patient rapidly grew weaker and became delirious; the pulse rate was rapid and the temperature was high. Rigidity of the neck developed, with vomiting; slight convulsions occurred and were followed by death.

Summary of the Gross Postmortem Observations (Dr. R. H. Jaffé).—Examination disclosed eclamptic nephropathy with hyaline thickening of the basement membrane of the glomerular tufts and swelling and slight proliferation of the glomerular endothelial cells; slight sclerosis of the afferent arterioles; hyaline droplet degeneration in some of the convoluted tubules (weight of the kidneys, 310 Gm.); periportal stasis and subcapsular hemorrhages in the liver (weight, 1,400 Gm.); softening of the splenic pulp (weight, 180 Gm.). The heart weighed 260 Gm. There was a diffuse colloid goiter, with a focal area of hyperplasia. There were petechial hemorrhages in the epicardium, pleura, mucosa of the stomach, cecum and renal pelvis. There was a puerperal uterus, with a retained placenta. The brain weighed 1,280 Gm. The leptomeninges were deeply congested, and the convolutions were slightly flattened.

Microscopic Postmortem Examination.—In general, the changes were similar to those in case 1 but more severe. Edema was marked, and the ganglion cells were more severely degenerated. Many cells appeared as shadows or were liquefied. Under a low power lens the cortex often appeared to be stained pale in streaks or spots, because of the degeneration or loss of ganglion cells. The Betz cells were more or less affected. In fact, degenerative changes of the

ganglion cells were observed in all parts of the brain—the basal ganglia, pons, medulla (olivary bodies) and Purkinje cells of the cerebellum. Neuronophagia and satellitosis were more or less in evidence. The oligodendrogliocytes were swollen and increased in number. A striking feature was marked hyperemia of all the blood vessels and capillaries, including those of the meninges. The lumens were packed with polymorphonuclears and lymphocytes, while some vessels appeared as if thrombosed, and others, especially larger blood vessels, occasionally exhibited mild perivascular lymphocytic infiltration. The smaller blood vessels and capillaries were hypertrophied, and their endothelial and adventitial layers were proliferated. The meninges over the cerebellum were hemorrhagic and contained numerous macrophages filled with blood pigment granules. In other areas the meshes were edematous and distended and contained many histiocytes, fibroblasts, mesothelial cells, lymphocytes and erythrocytes (fig. 6). The choroid plexus showed changes similar to those described in the previous cases.

CASE 5.—*Primipara; eclampsia; death eight days after appearance of first convulsion; minute multiple hemorrhagic foci in cerebral cortex; marked reactive phenomena of the microglia within and around foci; general increase in number of microglia cells; marked degenerative changes of ganglion cells; cerebral rarefaction and edema; cerebellar atrophy; reactive aseptic meningitis.*

History.—A white woman aged 19 was admitted to the Cook County Hospital on April 19, 1935, in a semicomatose condition and died on April 22. She was in her sixth month of pregnancy. Five days before admission she complained of severe headache and epigastric pain, followed by a convulsion which lasted for ten minutes. Four days later she had a second convulsion; this was followed by seven others.

Examination.—The patient was well developed and well nourished, and in a semicomatose state. The temperature was 100 F.; the pulse rate was 116, and the respiratory rate, 18. The blood pressure was 190 systolic and 120 diastolic. The usual eclamptic therapy was prescribed but with no improvement. The convulsions persisted. The urine was scanty and contained albumin, red blood cells, pus cells and casts.

Course.—The blood pressure fluctuated; at one time it fell to 120 systolic and 90 diastolic. Uterine contractions began, and there was spontaneous delivery of a dead fetus. For a short time the patient seemed to be better, but vomiting began and was followed by coughing and difficult breathing. The patient became cyanotic; the respiration was of the Cheyne-Stokes type. She went into a deep coma and died three days after admission to the hospital and eight days after the first convulsion.

Summary of the Gross Postmortem Observations (Dr. R. H. Jaffé).—Examination disclosed eclamptic nephropathy; anemia of the glomerular tufts and distinct thickening of the basement membrane of the tufts, which often appeared as a homogeneous band; slight thickening of Bowman's capsule; swelling of the glomerular epithelium; dilatation of the convoluted tubules, some of which contained casts of disintegrated red blood cells; slight thickening of the wall of the afferent arterioles, and small interstitial round cell infiltration at the corticomedullary border. The kidneys weighed 335 Gm. There was moderate dilatation of the left ventricle of the heart. The entire organ weighed 230 Gm. The liver (weight, 1,500 Gm.) was pale, with small hemorrhages underneath the capsule and on the surface of sections. The portal capillaries at the periphery of the lobules were greatly dilated; the spleen (weight, 105 Gm.) was soft. There was marked edema of the lungs and focal bronchopneumonia in the lower lobe of the

left lung. There was a puerperal uterus, with casts of decidual tissue. There was a cystic corpus luteum in the left ovary. The brain weighed 1,235 Gm. and was pale and moist but showed no other gross changes. The hypophysis measured 16 by 10 by 9 mm. and showed changes characteristic of gestation, with slight basophilic invasion of the posterior lobe.

Fig. 6 (case 4).—Aseptic meningitis. The subarachnoid space in the upper part of the section is dilated and greatly infiltrated with various cells, as described in the text. Toluidine blue stain.

Microscopic Postmortem Examination.—The noteworthy changes in this case were (1) minute multiple hemorrhagic foci scattered in the cerebral cortex and (2) marked reactive phenomena on the part of the microglia. In contrast to the

surrounding brain tissue, the foci appeared pale, swollen and edematous (fig. 7), with scattered areas of extravasated erythrocytes, especially around minute blood vessels. These minute vessels were markedly congested; some were plugged with hyaline thrombi; their walls were hypertrophied, and their endothelial and adven-

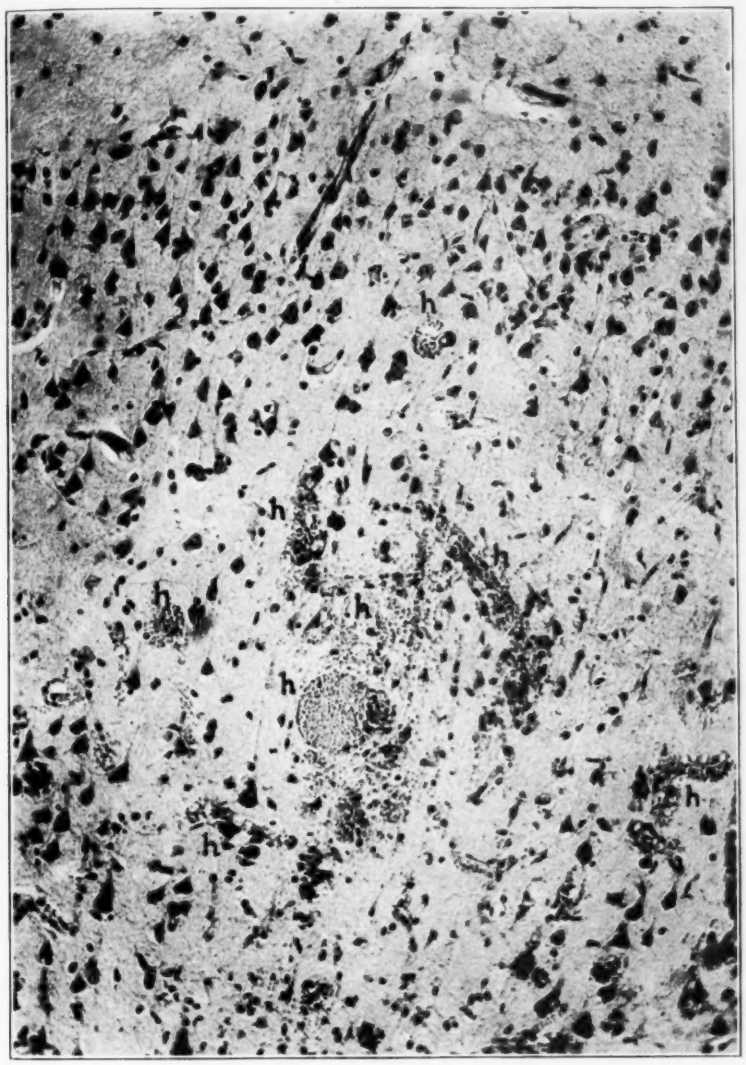

Fig. 7 (case 5).—Cerebral cortex. Minute hemorrhagic foci (*h*), showing marked reactive proliferation of microglia cells. Toluidine blue stain.

titial layers were proliferated. Mitotic figures were occasionally seen. The walls of some blood vessels appeared separated or disrupted, and their perivascular spaces were greatly dilated and invaded by red blood cells (ring hemorrhages).

As previously mentioned, a striking feature was the presence of numerous microglia cells within the foci and the adjacent areas (fig. 8). The cells varied

in size and shape. Many were elongated and sometimes resembled rod cells. However, their nuclei were more rounded, and their processes or dendrites were greatly swollen and reticular and contained vacuoles filled with erythrocytes (fig. 9).

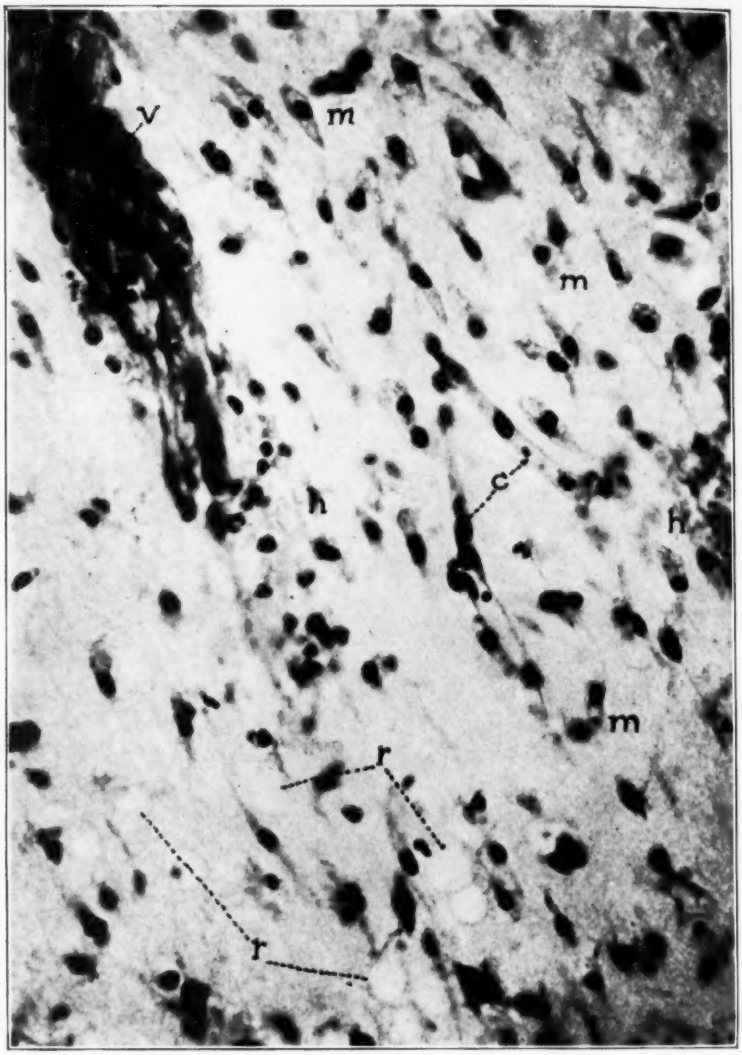

Fig. 8 (case 5).—Cerebral cortex, showing microglia cells (*m*) which are swollen; some are vacuolated around the foci of hemorrhages (*h*); disrupted blood vessels (*v*); capillaries (*c*), and edema and rarefaction of the parenchyma (*r*). Toluidine blue stain.

Other cells were irregularly shaped and possessed numerous branches, the body being somewhat round, much resembling an ordinary gitter cell. Although such cells varied greatly in structure, all unquestionably originated from microglia,

and their gradual transformation into gitter cells could be followed. A marked increase of the microglia, mainly of the rod cell type, was in evidence in this case throughout most of the brain.

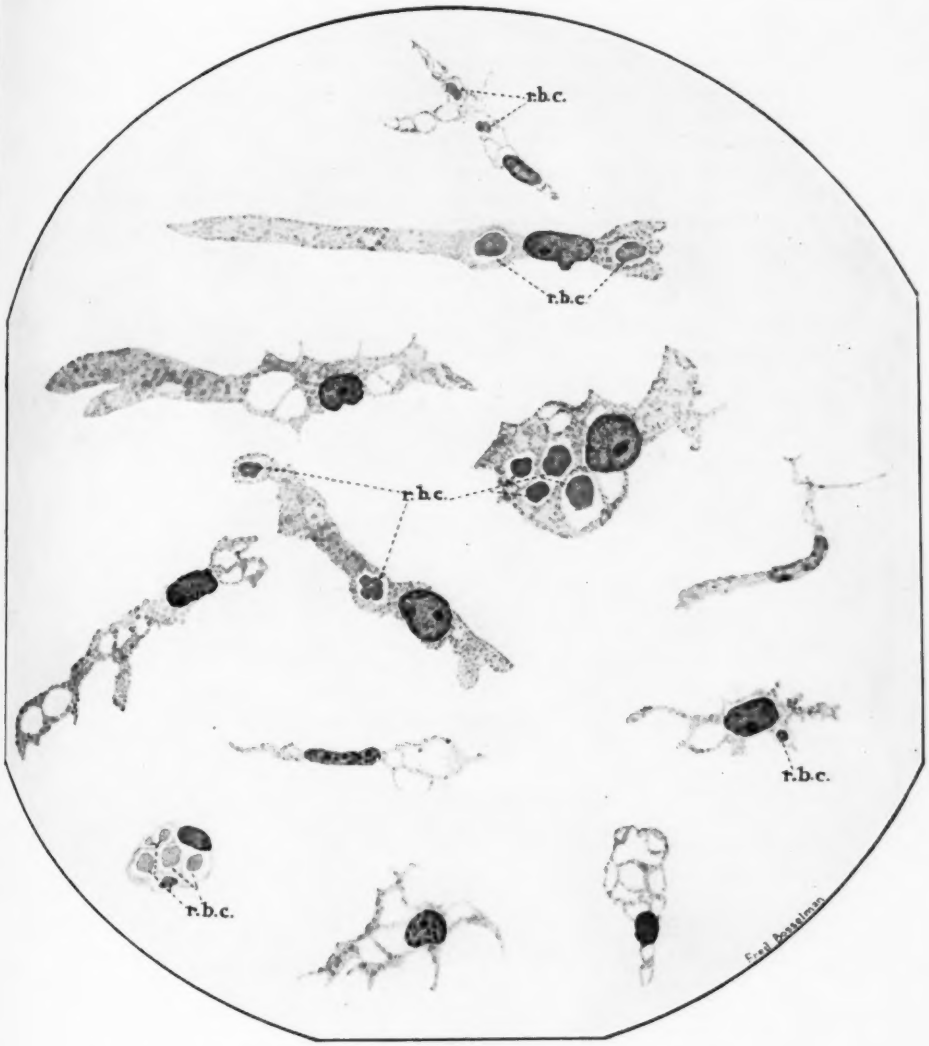

Fig. 9.—Microglia cells, showing red blood cells (*r.b.c.*) within their cytoplasm. Drawing made from the section shown in figure 7 under oil immersion magnification.

Aside from the foci described, the changes in general were not unlike those mentioned in the previous cases. The ganglion cells exhibited the so-called severe cell disease of Nissl, which was more marked in the cells within the foci and the adjacent areas. Edema and rarefaction were present throughout, especially within

the foci and around the blood vessels. The Virchow-Robin spaces were greatly dilated and were filled with a granular substance. They occasionally contained a red blood cell. The glia was proliferated throughout, as evidenced by the increased numbers of glia nuclei along the smaller blood vessels and capillaries.

The blood vessels and capillaries were congested; their walls were swollen and thickened, and the endothelial and adventitial layers were proliferated. Mitotic figures were occasionally seen, and newly formed capillaries were common.

A curious feature was atrophy of some of the leaflets of the cerebellum. In such leaflets the Purkinje cells, as well as the granular and molecular layers, were completely absent. The whole nerve parenchyma became transformed into a network of neurologial tissue and blood-vessel glial scar. The only cells in evidence were the glia cells of Bergmann. The granular layer exhibited no ganglion cells and consisted of numerous rod cells, astrocytes and newly formed blood vessels. The pia-arachnoid between these leaflets was hyperplastic and thickened. It was more or less distended throughout, especially in areas which exhibited marked hemorrhagic extravasation. Within its meshes there were many histiocytes, fibroblasts, small lymphocytes, polyblasts and numerous mesothelial cells. The vessels of the pia were greatly congested; some were filled with fibrin mixed with many polymorphonuclears, that is, were thrombosed.

The stroma of the choroid plexus was thickened and proliferated and contained many corpora arenacea. The blood vessels were congested, and the tuft cells were swollen, granular and frequently vacuolated.

SUMMARY AND COMMENT

Although the histologic changes in the brain in these five cases varied somewhat, they may be classified as general or diffuse and focal. The diffuse changes were more striking and were present in all five cases. They appeared as edema or rarefaction, degeneration of the ganglion cells and reactive phenomena in the glia, blood vessels and meninges. Focal changes were much less in evidence and were particularly marked in case 1, in which they showed as nodules (glial proliferation). However, in cases 1 and 4 the changes differed greatly from those in the other three. In these two cases the changes in the ganglion cells were somewhat severe. They were peracute, in the nature of liquefaction, and like other cell changes were scattered throughout the brain. Marked hyperemia with accumulations of leukocytes in the blood vessels and meningeal hemorrhages with lymphocytic infiltrations were the features in case 4 and may be considered as indicating a form of acute toxic meningo-encephalitis. This seems to be borne out by the clinical picture —high temperature, rigidity of the neck, vomiting, leukocytosis (38,750 leukocytes) and 90 cells in the spinal fluid.

In cases 2, 3 and 5 the general changes were associated with minute multiple degenerative lesions—softenings, sclerosis of the smaller blood vessels and minute and massive hemorrhages.

Of the changes described (general and focal), some may be considered fundamental; others, accidental or secondary. For instance, the nodules and perivascular infiltrations of the blood vessels, the thickening of the smaller blood vessels and especially the foci of degeneration and hemorrhages which have been repeatedly described (Schmorl,[1] Jaffé,[2]

1. Schmorl, W.: Zur Lehre von der Eklampsie, Arch. f. Gynäk. **65**:504, 1902.

2. Jaffé, Rudolph: Beitrag zur Frage der apoplektischen Blutung (an Hand eines Falles von Eklampsie), Zentralbl. f. Gynäk. **51**:1387, 1927.

Baird and Dunn [3] and others) are unquestionably secondary. Even the liquefaction of the parenchyma is not to be regarded as fundamental, for it evidently occurs only in fatal cases. Some changes are to be looked on as somewhat typical of eclampsia, whether mild or severe. These are rarefaction or edema of the cerebral parenchyma and changes in the ganglion cells and the subarachnoid space. These were present in every case studied and could be demonstrated in every part of the brain, in contrast to other changes—nodules, infiltration, softening and hemorrhages—which, as mentioned, were inconstant and must therefore be considered accidental.

The subarachnoid space was in all five cases greatly dilated and packed with abnormal cells—lymphocytes, polyblasts, mesothelial cells, fibroblasts and histiocytes; the blood vessels showed immense hyperemia and proliferation of their walls.

Such reactive phenomena, which may conveniently be termed aseptic meningitis, are not unlike those described experimentally by Ayer [4] and emphasized in human pathology by Hassin.[5]

If it is assumed that the toxins affect the brain directly, though probably not exclusively, causing the well known clinical symptoms, the involvement of the meninges should be considered a secondary process. To maintain that the involvement of the meninges also is the result of a direct action of the toxin would be illogical, as instances have not been described in human or experimental pathology of such a reaction of mesoderm to toxins. There are mesodermal changes to the action of lead, arsenic or other heavy metals, but such changes differ from those described in this paper.

The problematic toxins evidently invade the subarachnoid space and the meninges from the brain, which constantly discharges them by way of the Virchow-Robin perivascular spaces and thereby stimulates the cells to proliferation. The reaction of the subarachnoid cell elements should be considered secondary. The same may be said of the choroid plexus, in which the proliferation of the stroma also is to be looked on as secondary. The tuft cells were by no means normal, as they appeared swollen, granular and vacuolated and their nuclei were pyknotic.

As to the changes in the ganglion cells, they were not uniform. Such changes as liquefaction of the ganglion cells evidently occur, as has already been emphasized, but of course only in fatal cases. Those described by Spielmeyer [6] and his followers (Braunmühl,[7] Benoit,[8]

3. Baird, D., and Dunn, J. S.: Renal Lesions in Eclampsia and Nephritis of Pregnancy, J. Path. & Bact. **37**:291, 1933.

4. Ayer, J. B.: Pathological Study of Experimental Meningitis, New York, Monograph 12, Rockefeller Institute for Medical Research, 1912, p. 36.

5. Hassin, George B.: Histopathology of the Peripheral and Central Nervous Systems, Baltimore, William Wood & Company, 1933.

6. Spielmeyer, W.: Kreislaufstörungen und Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:536, 1930; The Anatomic Substratum of the Convulsive State, Arch. Neurol. & Psychiat. **23**:869 (May) 1930.

7. von Braunmühl, A.: Ueber Gehirnbefunde bei schweren Erregungszuständen, Ztschr. f. d. ges. Neurol. & Psychiat. **117**:163, 1928; Ueber

(Footnotes continued on next page)

Hechst,[9] Bodechtel[10] and others) as "ischemic and homogeneous cell disease" were observed only in cases 2 and 3. For this reason they should be considered accidental. When these changes are very severe they are associated with equally severe glial changes, as in case 2, in which they were ameboid.

A much more common and striking phenomenon was the behavior of the microglia. A marked reaction of the microglia was seen in every case, especially in case 5, in which, as the drawing shows, the microglia exhibited a remarkable phagocytic activity. The ubiquitous microglial changes, together with the other changes emphasized, may be considered morphologic manifestations of toxemia; that is, they denote severe toxemia. That eclampsia results from toxemia is generally admitted, regardless of the advocated theories and hypotheses of the causes of the toxemia. Thus, Williams[11] regarded eclampsia as a partial manifestation of a "general" toxemia. Goodall[12] saw the cause of toxemia of pregnancy in a diseased placenta and endocrine dysfunction. Hofbauer[13] first suggested that toxemia is due to hypersecretion of the posterior lobe of the pituitary gland. This theory is now accepted by many (Fauvet[14]), since the publication of the work of Anselmino, Hoffman and Kennedy.[15] They demonstrated an increased amount of antidiuretic and vasopressor principle (posterior lobe of the pituitary gland) in the blood of eclamptic patients. These substances cause retention of water, edema, inhibition of diuresis, capillary spasm and an increase in the blood pressure.

In recent years investigators have tried to explain the phenomena observed in eclampsia on the basis of Volhard's[16] theory of arterial spasm. Such vascular spasm, according to Volhard and others,[6] may result in the formation of diffuse and minute ischemic foci in the cere-

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Gehirnveränderungen bei puerperaler Eklampsie und ihre Entstehung durch Kreislaufstörungen, ibid. **117**:698, 1928.

8. Benoit, W.: Ein Beitrag zur Kenntnis der Rindenveränderungen bei Wochenbettseklampsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:602, 1931.

9. Hechst, Bela: Ueber Gehirnbefunde bei urämischen Zuständen, Ztschr. f d. ges. Neurol. u. Psychiat. **139**:544, 1932.

10. Bodechtel, G.: Hirnveränderungen bei den verschiedenen Formen der Urämie unter Berücksichtigung ihrer Pathogenese, Deutsches Arch. f. klin. Med. **174**:541, 1933.

11. Williams, W.: Obstetrics, ed. 6, New York, D. Appleton & Co., 1930.

12. Goodall, J. R.: Toxemia of Pregnancy, J. A. M. A. **105**:2121 (Dec. 28) 1935.

13. Hofbauer, J.: Die Aetiologie der Eklampsie, Zentralbl.f. Gynäk. **42**:745, 1918.

14. Fauvet, E.: Die Eklampsie, eine hypophysäre Erkrankung, Arch. f. Gynäk. **155**:100, 1933.

15. Anselmino, K. J.; Hoffman, F., and Kennedy, W. P.: The Relation of Hyperfunction of the Posterior Lobe of the Hypophysis to Eclampsia and Nephropathy of Pregnancy, Edinburgh M. J. **39**:376, 1932.

16. Volhard, F., in Mohr, L., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 1.

bral cortex, especially in the cornu ammonis, with loss and dropping out of the ganglion cells. It may also cause changes in the blood vessels and lead to hemorrhage and softening.

Bell [17] took exception to Volhard's theory of vascular spasm, as it does not seem to explain the thickening of the capillary basement membrane of the glomerular tufts present in eclampsia. He regarded the changes as a reaction to a toxic substance in the blood and described a case in which he considered that the condition was due to toxic myelitis.

The popular theory of vascular spasm cannot, like other theories and hypotheses, be either sustained or rejected on the basis of microscopic studies. Nor can Ricker's [18] theory—involvement of the neuromuscular apparatus of the blood vessels, resulting in the prestasis, stasis and poststasis phenomena—be sustained, for, like other hypotheses, it cannot explain the cerebral edema and rarefaction. The edema and rarefaction denote stasis of the tissue fluids, the inability of the brain to rid itself of the excessive accumulation of the fluids saturated with toxins. The excessive accumulation of tissue fluids is probably the result of the action of physicochemical factors or catabolic products that cause a disturbance in the water balance of the brain tissues. By influencing the osmotic and other physicochemical factors it is possible to reduce the edema successfully and with it the effects of intoxication. As a fact, the intravenous injection of hypertonic solutions is still one of the best methods of treatment, even in severe cases of convulsions in eclampsia. The most common features of eclampsia, as described in this paper—edema of the cerebral tissues, minute foci of softening and glial changes—are thus evidently the direct effect of toxemia on the central nervous system and also on the visceral organs through the action of the physicochemical products of a disturbed metabolism.

CONCLUSIONS

1. The changes in the brain in eclampsia are diffuse and focal.

2. The diffuse changes are more common. They include edema of the cerebral parenchyma, changes in the ganglion cells, a glial and microglial reaction and aseptic meningitis.

3. The focal changes are rare, occurring mainly as glial nodules.

4. The changes are similar to those present in severe toxic states in which there is a direct action of toxin on the parenchyma.

17. Bell, E. T.: Renal Lesions in the Toxemias of Pregnancy, Am. J. Path. **6**:1, 1932.

18. Ricker, G.: Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927.

SPECIAL ARTICLES

CORTICIFUGAL CONNECTIONS OF THE CEREBRAL CORTEX

A RÉSUMÉ OF EXPERIMENTAL INVESTIGATIONS

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AUGUSTA, GA.

In a series of articles I have reported [1] in detail the results of studies on the efferent fibers of the cortex of the brain of a primate (Macaca mulatta). After surgical removal of portions of the cortex the fibers arising from such an area were traced by the Marchi method [2] in complete serial sections.

Avoiding the specific details of the particular investigation, several rather general observations may be emphasized.

With regard to association fibers arising from any given point and ending within the same hemisphere, it may be noted that short association fibers do not arise, as one might suppose, from a given point and spread out fountain-like to all the surrounding cortex. On the contrary, the cytologic constitution of the neighboring cortex appears to play an important part in short association connections.

If, for example, only a portion of a cytologic area is removed, it is noted that the largest number of association fibers from the removed locus pass to the remainder of the cortex of the same type. I have used this intimate interrelation of points within a cytologic area as an illustration of the principle of the internal integrity of functional regions. The degree to which a point within a cytologic area is associated with points outside this area appears to have a parallel in functional association. Cortex which is primarily receptive (such as the striate cortex) does not send outside itself as many association fibers as the parareceptive

From the Department of Anatomy, University of Georgia School of Medicine.

1. Mettler, Fred A.: Brain of Pithecus Rhesus (M. Rhesus), Am. J. Phys. Anthropol. **17**:309, 1933; Fiber Connections of Pithecus Rhesus, Anat. Rec. (supp.) **55**:67, 1933; Corticifugal Fiber Connections of the Cortex of Macaca Mulatta: The Occipital Region, J. Comp. Neurol. **61**:221, 1935; The Frontal Region, ibid. **61**:509, 1935; The Parietal Region, ibid. **62**:263, 1935; The Temporal Region, ibid. **63**:25, 1935.

2. Mettler, Fred A.: Marchi Method for Demonstrating Degenerated Fiber Connections Within the Central Nervous System, Stain Technol. **7**:95, 1932.

tive cortex (such as the peristriate and parastriate cortex) which surrounds it. It is the latter type of cortex which is designated sensoripsychic (visuopsychic in this instance); Flechsig's[3] term association area for these regions is of course familiar and is useful, though not without its limitations. It is decidedly more useful than the term silent area, which was based on the erroneous belief that such an area is innocent of projection fibers. Parareceptive cortex shows strong associational connections with its related primary receptive cortex and a well marked tendency to associate with the motor cortex, particularly with the motor points of most significant physiologic association (such as connections from the temporal parareceptive cortex to the motor points for the eye and the hindlimbs). These generalities as to functional parallelism can be supported by interesting details: Thus, the upper (dorsal) parareceptive occipital region (which is related to the upper retinal field) has better developed associational connections than the lower region. The majority of daily visual perceptions, of course, fall on the upper part of the retina. An important detail in conjunction with short association fibers, which should be mentioned, is that by the Marchi method the existence of the time-honored U-shaped fibers can be proved beyond doubt. Rosett,[4] in his excellent monograph, tended to minimize these connections. This is probably the fault of the technic used, which presumably makes it difficult to see them, but even from small lesions caused by pressure placed at the summit of a gyrus, delicate degenerated medullated fibers can clearly be seen to swing down through the medullary core and up into neighboring gyri. This also argues for the origin of these association fibers from the superficial cortical layers.

In this particular primate the number of well organized bundles of long association fibers was limited. Distinction between long and short association fiber systems appears to be rather arbitrary, since many so-called long association systems (i. e., cingulum) are really composed of rather short fibers which mechanics of growth (in the case of the cingulum the corpus callosum is probably the factor responsible) have forced into more or less well-defined bundles.

The callosal connections of the cortex follow a generalization which, for want of a better term, I have called the principle of heterolateral cortical callosal association. According to this view, if a point A is strongly associated with points B, C and D, located in the same hemisphere, but only sparsely with points E and F, also located there, then its callosal connections pass to the homologous points A^1, B^1, C^1, D^1, E^1

3. Flechsig, P.: Ueber ein neues Eintheilungsprincip der Grosshirnoberfläche, Neurol. Centralbl. **13**:674, 1894.

4. Rosett, J.: Intercortical Systems of the Human Cerebrum, New York, Columbia University Press, 1933.

and F^1 in the opposite hemisphere, the first four of which are strongly connected to point A and the last two only sparsely connected.

It early became evident in this work that the division of cortex into types I and II of Flechsig was not sufficient for a proper understanding of the fibers arising from the cortex. According to Flechsig's classification, type I cortex includes that which either receives sensory radiations or gives rise to projection fibers, while type II is distinguished by the absence of such fibers. Type II cortex under this nomenclature gives rise only to association fibers and constitutes what have been termed association areas. My observations, however, indicate that a large part, if not all, of type II cortex gives rise to corticifugal fibers, many of which end in the striatum, diencephalon, pons or brain stem. I have also noted that some fibers of this short subcortical type arise in Flechsig's type I cortex (which I call primary receptive, or emissive, cortex). Most of them, however, come from parareceptive cortical belts immediately surrounding the primary receptive areas.

From the occipital region, fibers pass to the lateral geniculate body. Most of them arise from the peristriate and parastriate cortex (which forms the parareceptive belt surrounding the primary receptive visual region, the striate cortex), run into the pulvinar, which they penetrate, and end in the geniculate body. The entire temporal region sends fibers to the medial geniculate body. The disparity in the number of fibers arising from the circumambient and primary receptive area is not as pronounced as in the case of parareceptive (peristriate and parastriate cortex) and receptive (striate) areas in the occipital region, but a disparity exists. Coming through the internal capsule, these fibers form a cap over the lateral geniculate body and then sweep into the medial geniculate body.

The cortex surrounding the striate area on the lateral surface of the brain sends fibers to the pulvinar. Although the striate area sends fibers through the pulvinar in certain places, it is doubtful that any of these end in this structure. One component of this group passes into the central gray matter of the aqueduct and the region of the posterior commissure, while another component ends in the vicinity of termination of the optic tract in the superior colliculi (other parts of frankly parietal cortex also contribute fibers to the pulvinar).

The entire parietal and upper temporal regions and the cortex of the precentral (gyrus) region send fibers to the lateral nucleus of the thalamus. The fibers reach this structure via the internal capsule, from which they swing medially into the lateral thalamic nucleus.

The superior colliculus receives fibers from two cortical loci. One exists in the caudal end of the middle frontal gyrus and the adjacent region of the precentral gyrus. The fibers penetrate the area of junc-

tion of the lateral thalamic nucleus and pulvinar. The second set of fibers comes from the region immediately surrounding the striate area, penetrates the ventral part of the pulvinar and reaches the tectum in the brachium of the superior colliculus. Probably no part of the striate cortex itself sends out corticotectal fibers. The inferior colliculus receives fibers from the temporal region. These fibers sweep into the tectum from the region of the lateral lemniscus, which it reaches by passing ventrally through the pulvinar.

Not only by means of the corticobulbar tract, which arises from the ventral portion of the precentral gyrus, do the motor eye nuclei receive fibers, but also from the temporal area (traveling in association with the lateral lemniscus), from the region surrounding the striate area (as fibers associated with the medial lemniscus) and from the middle and inferior frontal gyri. The latter fibers are not part of the corticobulbar tract but reach these nuclei by traveling in the medial lemniscus and tegmentum. They go especially to the oculomotor, interstitial, trochlear and abducens nuclei. It will be observed that the upper eye nuclei are reached by a variety of fibrous offsets, but the lower nuclei are reached more particularly by fibers in association with the medial lemniscus.

From the base (ventral portion) of the precentral gyrus, cortical fibers pass to the inferior olives. These structures also receive fibers from the cortex situated in the parietal region. The olives are reached by a fasciculus made up of two components: One of these is a condensation of diffuse tegmental degeneration; the other is an accumulation of fibers which swing out from the medial part of the peduncle. Although most of these fibers swing into the olivary sac, some are grouped around the other portions of the olive, including the accessory and medial segments.

The tegmental nuclei receive fibers from the cortex of the temporal region. I [5] have already described these fibers in the cat, as they sweep dorsally from the peduncles. In the monkey these nuclei, as well as the trigeminal nuclear complex, receive fibers from the parietal and temporal regions and also from the ventral half of the precentral gyrus (which, in addition to the fibers in the peduncle, sends fibers to the trigeminal complex in the medial longitudinal fasciculi of both sides) and the middle and inferior frontal gyri. Some of the fibers from the precentral gyrus pass to the central trigeminal nucleus of the opposite side by decussating with the cerebrospinal tracts. There is also an upper

5. Mettler, Fred A.: Connections of Auditory Cortex of the Cat, J. Comp. Neurol. **55**:139, 1932.

decussation. The facial and hypoglossal nuclei also receive fibers of cortical origin. The vagal nucleus receives fibers which probably come from area 4 (the motor area).

From the middle and inferior frontal gyri, as well as from the parietal and posterior temporal regions, fibers of large caliber pass to the substantia nigra via the cerebral peduncle. Corticonigral fibers were described originally by Schukowski.[6] They go especially to the pars diffusa.

One of the most significant of the corticifugal systems is the cortico-pontile fiber groups. Fibers arise from the posterior part of the parietal region, the posterior and ventral portions of the temporal region and the middle and inferior frontal gyri and pass to the pontile nuclei by way of the cerebral peduncles. From this point it is known that fibers arise which pass by way of the brachium pontis to the cerebellum.

The middle and inferior frontal gyri, the ventral portion of the parietal area and most of the temporal area give rise to fibers which go to the subthalamus as penetrating fibers of the globus pallidus and partially as fibers accompanying the thalamic fasciculus. The nucleus of the ansa peduncularis receives fibers from the middle third of the precentral gyrus.

Although the presence of fibers passing as an independent system from the cortex to the caudate nucleus has been specifically denied by physiologists, my work shows the existence of such a connection. These fibers arise from the frontal area and travel in the subcallosal fasciculus of Muratoff, reaching the caudate nucleus by way of the basal part of this bundle. The claustrum also receives fibers from the frontal region, which are intermingled with the short association fibers.

The hypothalamus (particularly the region of the periventricular fiber system) and the septal (septohypothalamic nuclei) region receive fibers from the precentral as well as from the parietal region. The possible importance of such fibers in providing a cortical effect on autonomic functions has been discussed by Kuntz.[7]

The cortex bordering the central fissure just posteriorly, as well as anteriorly, sends fibers (corticorubral fibers of Monakow) to the red nucleus, which also receives fibers (corticorubral fibers of Monakow) from the temporal region and from the middle and inferior frontal gyri. These connections are mediated by fibers in the fasciculus lenticularis and have a bilateral distribution by way of the commissure of the red nuclei.

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6. Schukowski, N.: Ueber anatomische Verbindungen der Frontallappen, Neurol. Centralbl. **16**:524, 1897.

7. Kuntz, A.: Autonomic Nervous System, Philadelphia, Lea & Febiger, 1934.

COMMENT

It is now recognized that the extrapyramidal as well as the pyramidal system has a cortical representation [8] from the physiologic standpoint. In addition, the idea of cortical representation of the autonomic system is by no means novel.[9] Although older investigators explained these effects to their own satisfaction, English and American workers of the present time, with a few notable exceptions, seem unconvinced. Redemonstrations are again being reported, and with support of anatomic demonstration the results may win a more permanent place. It is interesting to speculate what effect this will have on modern views of clinical conditions, especially epilepsy.

Lately, in conjunction with Culler, I have observed currents of action in the autonomic system which are elicited by stimulation of the cortex; with Krafka, Combs, Spindler and Mettler,[10] disturbance in hematopoiesis following cortical injury, and, with Hamilton, Allen, Woodbury and Mettler,[11] cardiac and blood pressure effects of a nature indicating that stimulation of the cortex is capable of exciting both the sympathetic and the parasympathetic system, the action of the latter being under usual circumstances completely obscured by the effects of the action of the former. Pupillary, gastro-intestinal, motor and secretory motor effects can also be produced. A growing interest in the extrapyramidal and autonomic functions of the cortex appears in my mind to justify the investigation of the fiber connections here presented. Except in a few isolated instances, the corticifugal types described have been mentioned at some time or other in the literature. Owing to the absence of confirmation and the lapse of years, several reports have failed to appear in works of reference.

My work is interpreted as indicating the existence of an elaborate series of cortical connections with subcortical centers, many of which

8. Wiggers, C. J.: Physiology in Health and Disease, Philadelphia, Lea & Febiger, 1934.

9. Schiff, M.: Lezioncina di fisiologia sperimentale, Florence, E. & F. Cammelli, 1873. Richet, C.: Des circonvolutions cérébrales, Paris, Germer-Baillière & Cie, 1878. François-Franck, C.-E.: Leçons sur les fonctions motrices du cerveau et sur l'épilepsie cérébrale, Paris, O. Doin, 1887. Couty, A.: Sur le cerveau moteur, Arch. de physiol. norm. et path. **15**:257, 1883.

10. Combs, J. D.; Mettler, F. A.; Spindler, James, and Mettler, Cecilia C.: Disturbances in Autonomic Function Following Localized Cortical Ablations, Anat. Rec. (supp.) **61**:11, 1935. Combs, J. D.; Mettler, Cecilia C.; Krafka, Joseph, Jr., and Mettler, F. A.: Effects of Cortical Removal upon Hematopoiesis and Gastric Activity, Anat. Rec. (supp.) **64**:9 (March) 1936.

11. Mettler, C. C.; Hamilton, W. F.; Allen, Lane; Woodbury, R. A., and Mettler, Fred A.: Influence of the Cerebral Cortex upon the Cardiovascular System, Anat. Rec. (supp.) **64**:33 (March) 1936.

are motor. These corticifugal fibers arise not only from the frontal area but also from the cortex in association with the primary receptive areas. A possible mechanism therefore exists for affecting the final common path after segmental reflexes have been brought about and at the same time as, or before, pyramidal effects are manifested.[12] It need not be that the corticifugal fiber connections here described are all concerned with somatic motor effects, since mechanisms are presented by which visceral motor centers may also be influenced.

12. Barker, L. F.: On a Striato-Pallido-Nigro-Thalamic Syndrome, Internat. Clin. **1**:1, 1929.

News and Comment

NEW ENGLAND SOCIETY OF PSYCHIATRY

At the annual meeting of the New England Society of Psychiatry at the Gardner State Hospital on April 22, 1936, with Dr. Horace G. Ripley, of Vermont, president, in the chair, the following physicians were elected to active membership: Dr. Maudie M. Burns, Middletown, Conn.; Dr. Edwin M. Cole and Dr. Merrill Moore, Boston; Dr. Salvador Jacobs, Danvers, Mass.; Dr. William J. Johnson, Wrentham, Mass.; Dr. Fernand Longpre, Northampton, Mass., and Dr. Hosea W. McAdoo, Arlington Heights, Mass. Officers elected for 1936-1937 were: president, Dr. Winfred Overholser, Boston; vice president, Dr. Chester Waterman, Norwich, Conn.; secretary-treasurer, Dr. Harlan L. Paine, North Grafton, Mass.; councillors, Dr. Arthur P. Noyes, Howard, R. I., and Dr. Roderick B. Dexter, Foxboro, Mass. Annual awards for the best papers based on research in psychiatry completed during 1935 were made to: Dr. Benjamin Cohen, of the Grafton State Hospital, for his paper "Repression and Communicability in Catatonic Stupor"; Tamara Dembo and Eugenia Hanfmann, of the Worcester State Hospital, for their paper entitled "The Patient's Psychological Situation upon Admission to a Mental Hospital," and Drs. Benjamin Simon, of the Worcester State Hospital, and Philip Solomon, of the Boston Psychopathic Hospital, for their paper on "Multiple Sclerosis." Dr. Abraham Myerson, of Boston, delivered an address on "The Neuroses."

FIRST INTERNATIONAL CONFERENCE ON FEVER THERAPY

The First International Conference on Fever Therapy will be held at Columbia University, New York, from March 30 to April 2, 1937. The subjects to be discussed will include physiologic and pathologic changes in and the treatment of gonorrhea; gonorrheal and nonspecific arthritis; syphilis in its various stages; neurologic conditions, such as multiple sclerosis, chorea, dementia paralytica and tabes; cutaneous diseases, and other diseases. The chairman is Baron Henri de Rothschild of Paris, France. The French Committee, of which Professor d'Arsonval is honorary president, is under the chairmanship of Professor Abrami. Other members of this committee include Profs. Alajouanine, Binet, Claude, Janet, Lardennois, Laubry and Levaditi, and the general secretaries of the committee, Drs. Halphen and Auclair. The American Committee consists of Drs. Desjardins, Bierman, Hartman, Hinsie, Neymann, Simpson and Warren. National European committees are being formed under the direction of Profs. Maranon of Spain, Frugoni of Italy, Volhard of Germany, Wagner-Jauregg and Eppinger of Austria, Michaux of Switzerland, Bessemans of Belgium and Danielopolu of Roumania. Abstracts of the papers read will be published in a volume of the transactions in English, German and French. Information regarding this conference may be secured from the general secretary, Dr. William Bierman, 471 Park Avenue, New York.

Obituaries

JOHN JENKS THOMAS, M.D.
1861–1935

A biographic account of the life of Dr. John Jenks Thomas is a history typical of men who have figured prominently in the building up of American medicine. There is first a sound and thorough training; this is followed by a prodigious amount of hospital work and a continued connection with a medical school, through which a profound influence is exercised on the young men who enter the field of medicine. To this is added consultation work, and thus the men in practice are kept in touch with progress in the consultant's chosen field of medicine.

Dr. Thomas was 74 years of age on the date of his death, July 17, 1935. He graduated from Williams College in 1886 and received the degree of M.D. from the Harvard University Medical School in 1890. He married Frances Pickering Walker in 1899, and they had three sons and one daughter. He served in the World War with distinction and amazed his colleagues by his strength and endurance, which was in striking contrast with his small and apparently frail body. He became a member of the American Neurological Association in 1895 and was vice president in 1908 and in 1916. He was president of the Boston Society of Psychiatry and Neurology in 1911. He was a zealous attendant of the meetings of these societies, and his interest in the papers read continued to the time of his death.

His connections with three institutions mark milestones in the history of neurology in those institutions. For forty years, from 1887 to 1927, he was in the neurologic division of the Boston City Hospital, and for many years he was its head. He was intimately connected with the department of neurology of the Boston Children's Hospital. He was an assistant professor when Dr. Morton Prince was professor of neurology of Tufts College Medical School and later became full professor and head of the department. There are five men whose names can be intimately linked with the development and organization of neurology in Boston and thus in America—Drs. Morton Prince, Philip Coombs Knapp, J. J. Putnam, E. W. Taylor and John Jenks Thomas.

I shall never forget the impression made on me at the very beginning of my medical career by the thoroughness, the patience and the calm imperturbable tenacity of approach characteristic of Dr. Thomas' neurologic studies. When Dr. Thomas started his work, and for a large part of his career, there were no roentgenographic studies to help in diagnosis. Lumbar puncture was just beginning to be used and did not reach routine application until late in Dr. Thomas' career. The

Wassermann test was unknown, and diagnosis rested on an acumen of observation and an evaluation of details which are not so necessary at the present time. Now a diagnosis of dementia paralytica can be made from the laboratory record. An encephalogram carefully studied may locate a tumor of the brain. The laboratory report may contain in its essentials the grounds for a diagnosis. In 1907, when I first came under the influence of Dr. Thomas, physical examination and history were, practically speaking, the totals of diagnostic information. Everything the patient did or said, from his manner to the details of his gait, were noted by Dr. Thomas. His students and those associated

JOHN JENKS THOMAS, M.D.
1861-1935

with him received a grounding in neurologic technic which never lost its importance. Examination of the reflexes was approached with deliberation; the patient was posed with exactness; the place where the hammer was to impinge was selected, and there was almost a ritual of study involved in this relatively simple matter. The pupils had to be studied with exactness. The sensory examination was made with a thoroughness and psychologic acumen which merited the term "artistic." Dr. Thomas was quick and sharp in his manner, yet in his approach to a patient was kindness itself; though he was busy he never seemed hurried, either in his examination or in the therapeutic instructions which he gave to the patient.

Dr. Thomas did not cling to the old when the newer instruments of procedure were instituted. He learned about the newer technics and applied and encouraged their use in his service. He lived to see the day when the neurologic service, which was the underdog of all the services at the Boston City Hospital, obtained recognition and finally achieved a dignity and importance second to none. He was instrumental in bringing it about that every man practicing medicine must learn neurology as part of the approach to a patient's problem.

Neurology passed from empiricism to science during his lifetime. It passed from an incidental subject to one of major importance in the training of medical men. To both of these progressive efforts Dr. Thomas lent the strength and energy of his steady and active mind.

ABRAHAM MYERSON, M.D.

HERMAN M. ADLER, M.D.
1876–1935

Dr. Herman M. Adler died of pneumonia at the Massachusetts General Hospital on Dec. 6, 1935, at the age of 59. He was the son of a prominent physician in New York. He was graduated from the Harvard University Medical School and served as neuropathologist at the Danvers State Hospital, in Massachusetts, prior to joining the staff

HERMAN M. ADLER, M.D.
1876-1935

of the Boston Psychopathic Hospital. He soon became chief of that staff.

In 1916 Dr. Adler was brought to Chicago to make a survey of mental health in that city. With the departure of Dr. William Healy for Boston, Dr. Adler succeeded him as director of the Chicago Juvenile Psychopathic Institute. Within a few months, with the reorganization of public welfare work in Illinois, he was appointed criminologist of

the state department of public welfare. Except for the period of his service in the World War, 1917-1918, in which he took an active part in the formulation and evaluation of methods of study of intelligence in the army, he continued to serve as criminologist and director of the institute, control of which, through his efforts, was transferred from the county to the state under the new title of Institute for Juvenile Research, until his resignation in December 1929. At that time he assumed the combined duties of consultant to the department of public welfare of California and professor of the University of California at Berkeley. He was brought to the university for the purpose of creating a department of criminology. In the face of many obstacles and great difficulty he saw this work fully developed.

Dr. Adler will be best remembered by the members of the various professional societies to which he belonged as a thoroughly scientific worker, an intelligently honest man and a clear thinker, who was fearless in support of his convictions. The large number of these societies gives evidence of the high regard in which he was held. Throughout the years of his work in three areas, extending over the entire country, Dr. Adler's clear thinking was felt by all who came in contact with him. He is probably best known for the development of the program of the Illinois Institute for Juvenile Research, for which he received not only national but international recognition. His numerous publications in diversified fields give evidence of his originality and critical creative thinking and will serve as memorials to his work.

PAUL L. SCHROEDER, M.D.

MORTIMER WILLIAMS RAYNOR, M.D.
1879–1935

With the death of Dr. Mortimer W. Raynor on Oct. 5, 1935, there passed from the medical group of the state of New York a psychiatrist who in a quiet, unassuming way had been a pioneer in modern psychiatric treatment. All his interest had been devoted to the furthering of psychiatric care during his entire medical life.

Dr. Raynor was born in Syracuse, N. Y., on June 20, 1879. After a preliminary education in the schools of Syracuse he was graduated from the Syracuse University College of Medicine in 1904. From 1904 to 1907 he served as intern, first in the Newark City Hospital and later in the Kings County Hospital in Brooklyn. From there he went directly into psychiatric work in the Hudson River State Hospital in Poughkeepsie. He was advanced from junior assistant physician to senior assistant physician in the next five years, which title he held until February 1917.

At this time the department of corrections of the city of New York decided to found a psychiatric clinic in connection with the penitentiary on Blackwell's Island. This was a new departure which called for a psychiatrist with a special type of ability and a special type of personality to deal with the difficult problems of one of the most difficult city prisons in this country. It was not by chance that the choice fell on Dr. Raynor as a man well fitted to make a success of a venture that was considered most questionable by some older penologists. He did make a success of it, but resigned in August 1917 to enter the United States Army. As a captain in the medical corps, he was assigned to Camp Meade, until he joined the Seventy-Ninth Division as division psychiatrist in January 1918. One month later he received the commission of major. On July 8, 1918, he left for France with his division and served with them through their campaign until the armistice. He was cited "for services during the offensive against Montfaucon and Nantillois, Sept. 26-30, 1918." He returned home in January 1919 to take up his work in the New York state hospitals, now as director of clinical psychiatry in the Manhattan State Hospital on Ward's Island. While in this position he organized and put into operation one of the first general diagnostic clinics to be established in a state hospital and one which has since served as a model.

In May 1924 he was appointed superintendent of the Kings Park State Hospital. He held this position until he became medical director of the Bloomingdale Hospital at White Plains, N. Y., in September 1926. Here again he found himself in a position which required unusual

talents for organization. This hospital, one of the oldest hospitals for patients with mental diseases in the country, has had a noteworthy history of achievement. It had as its heritage all of the advantages of the prestige of its honorable past and not a few of the disadvantages of age in institutions. Dr. Raynor's work was to make it a modern hospital, and his work may be judged by the record of the hospital in the past nine years. Under his guidance the hospital concentrated on curative rather than custodial care and this end was attained by stressing not only psychiatric care but medical and surgical diagnosis and care as well as the development of a social environment that would be conducive to recovery of patients with mental diseases. He was still working on improvement at the time of his death.

Always modest and retiring, with a tendency, almost constitutional, to "put his candle under a bushel," Dr. Raynor nevertheless received recognition from his colleagues in and around the city of New York. This recognition took form in his election to the presidency of the New York Society for Clinical Psychiatry, the New York Psychiatric Society and the Westchester County Medical Society and as chairman of the Executive Committee of the New York State Committee of Mental Hygiene.

Dr. Raynor was a psychiatrist with the spirit of a pioneer, but first of all he was a physician. To him a patient presented a medical problem, always to be treated as such. He was one of those unobtrusive organizers under whose kindly, sympathetic hand things always seemed to run right. His luck was the luck of sincere friendship, which he gave and attracted. Those who value him most are those who knew him longest.

LOUIS CASAMAJOR, M.D.

Abstracts from Current Literature

Physiology and Biochemistry

THE ANTINEURITIC VITAMIN: V. THE PREPARATION OF A VITAMIN CONCENTRATE SUITABLE FOR PARENTERAL USE. E. H. STUART, R. J. BLOCK and G. R. COWGILL, J. Biol. Chem. **105**:463, 1934.

The authors have succeeded in producing an inexpensive, easily prepared vitamin B (B_1) solution suitable for parenteral use in man by adsorption of the vitamin on a definite amount of Lloyd's reagent and subsequent elution with warm alcoholic hydrochloric acid. They describe the method in detail for preparation of a reagent containing 0.25 international unit per milligram of solids. This can be further purified to contain 2.5 international units per milligram from which a vitamin solution can be eluted which contains about 5 international units per milligram of total solids.

IRVINE, Boston.

STUDIES ON THE ADRENAL: VII. A SIMPLE PREPARATION OF THE ADRENAL CORTICAL HORMONE SUITABLE FOR ORAL ADMINISTRATION. ARTHUR GROLLMAN, W. M. FIROR and ELLIS GROLLMAN, J. Biol. Chem. **109**:189, 1935.

Clinical studies regarding the effects of adrenal cortical hormone in morbid states have been seriously hampered by the lack of easily available, potent preparations. Grollman, Firor and Grollman found that such preparations can be made by adsorbing on charcoal the hormone from extracts of adrenal glands. Frozen pig's glands were extracted with acetone which had been chilled to remove most of the lipid. The filtrate was subjected to vacuum distillation to remove the acetone. The aqueous residue was neutralized, and activated charcoal was added. It adsorbed the hormone, and after preliminary washing the charcoal-hormone combination was suitable for oral administration.

Adrenalectomized rats and dogs were kept alive and free from symptoms as long as cortical hormone was fed in their food, but they died with typical signs of adrenal insufficiency if it was withheld. It was found that the charcoal preparation fed to rats by mouth was as efficacious as adrenal extract injected intraperitoneally. Perhaps the efficacy of this preparation over other adrenal extracts prepared for oral administration is due to the slow and complete liberation of the hormone by the action of intestinal juices.

PAGE, New York.

THE EFFECT OF THYROID AND THYROXINE ON THE CONCENTRATION OF CREATININE IN THE HEART, MUSCLE, LIVER, AND TESTES OF THE ALBINO RAT. MEYER BODANSKY, J. Biol. Chem. **109**:615, 1935.

Creatine (methylguanidine acetic acid) is unevenly distributed in the body, about 98 per cent of the total occurring in the muscles and most of the remainder in the gray matter of the brain and in the testes. In combination with phosphoric acid it is intimately concerned with the liberation of energy in muscle. Bodansky has independently confirmed the observation of Cowan that the administration of thyroid substance or synthetic thyroxine to rats resulted in a marked reduction of the creatine content of the heart. Even more striking was the depletion of phosphocreatine. Other workers have observed the same in rabbits and in guinea-pigs. Not infrequently death occurred in a manner suggestive of cardiac failure. These results suggest that the disappearance of phosphocreatine from the myocardium may be related to heart failure in cases of acute thyrotoxicosis.

PAGE, New York.

THE EFFECT OF TEMPERATURE ON OSMOTIC EQUILIBRIUM OF LIVING CELLS (UNFERTILIZED EGGS OF ARBACIA PUNCTULATA). BALDWIN LUCKÉ, J. Cell. & Comp. Physiol. **5**:465, 1935.

No effect of temperature on cell volume was demonstrated (lowest temperature, 5.4 C.; highest, 29.3 C.). Temperature over the range employed has no effect on the position of osmotic equilibrium of the egg of Arbacia punctulata.

CHORNYAK, Philadelphia.

EXPERIMENTAL INNERVATION OF MUSCLES BY THE CENTRAL ENDS OF AFFERENT NERVES (ESTABLISHMENT OF A ONE-NEURONE CONNECTION BETWEEN RECEPTOR AND EFFECTOR ORGAN), WITH FUNCTIONAL TESTS. PAUL WEISS, J. Comp. Neurol. **61**:135 (Feb.) 1935.

Experiments were conducted to see if a sensory nerve supplying a denervated muscle transplant could have a motor function. The experiments consisted in: (1) severing a dorsal root at its entrance into the cord and inserting it into a transplanted muscle, thereby creating a direct connection, by a single neuron, between a receptor and an effector organ; (2) testing the fate of adequate sensory excitation in such a mononeuronal system; (3) testing, by electrical stimulation, whether the dorsal root had succeeded in forming functional connections with the muscles and furthermore whether electrical stimulation of the nerve on the one hand and natural stimulation of the sense organs on the other would give the same or different functional results, and (4) examining histologically the fate of the dorsal roots in the muscles and the manner in which neuromuscular connections were established. The common toad was used. Sixteen successful operations were performed. The connection between the muscle and its new nerve supply was examined both physiologically and histologically. In a number of cases the dorsal root fibers formed functional connections with the muscle fibers. This confirms the view that in the formation of nervous connections with peripheral organs no strict selectivity exists. In cases in which the experiments were successful electrical stimulation of the sensory nerve yielded prompt and vigorous contractions of the muscle connected with its central end. In sharp contrast to the positive effect of electrically evoked excitations, the adequate sensory excitations evoked by mechanical stimulation of the sense organs failed consistently to contract the muscles. The author explans this difference in results as the "resonance principle."

ADDISON, Philadelphia.

STUDIES ON LANGUAGE IN THE CHILD. ANDRÉ OMBREDANE, Hyg. ment. **30**:69 (April) 1935.

The cry of the new-born infant is a local manifestation of a generalized reaction of defense, tonic in character. The first lallings bear the stamp of a tonic activity. They occur under conditions of resistance to the infant's reactions or with movements giving an attitude of hyperextension. They may be looked on as tonic postural reflexes. Occlusion of the glottis is a primary element of all these reactions of generalized muscular tension. Gradually labial phenomena become more important, and as their dominance commences the period of cortical functioning sets in. Imitation is now the order of the day; the guttural phenomena occurring in this stage are not the same as the glottic lallings of the earlier tonic period.

ANDERSON, Los Angeles.

THE FEELING OF TIREDNESS. L. R. MÜLLER, Deutsche Ztschr. f. Nervenh. **135**:211 (Feb.) 1935.

Müller observes that although students of physiology have paid much attention to fatigue of the nerves and muscles, little is to be found in the literature on the feeling of bodily tiredness. Müller does not refer to localized painful sensations

following excessive bodily activity, such as painful sensations in the legs after a long march or other similar excessive bodily activities, but refers to general bodily tiredness. He denies that tiredness is caused by the production of fatigue toxic substances (kenotoxin). He likewise refutes the assertion that lactic acid developed during muscular activity is responsible for the tired feeling. This acid, he says, is again changed by means of oxidation into glycogen, the remainder being burned into carbonic acid and water. However, Müller concedes that under the influence of protoplasmic acidity, electrolytic splitting of the salts and increased permeability of the cell membrane, which permit extravasation into the lymph stream of the calcium, potassium and magnesium cations, the irritability of the nerve cells is lowered and thus a feeling of tiredness is produced.

Although tiredness cannot as yet be explained on a physicochemical basis, it can be recognized by the facial expression, by the manner in which the bodily movements are executed and by the slow, dragging gait. Mentally it expresses itself by slowing of psychic reactions, dulling of memory, slowing of speech and diminished intellectual power. The feeling of tiredness appears only after consciousness of a lowered physical and mental state. One can overcome a tired feeling by strong mental effort. Tiredness is a physicochemical process; the feeling of tiredness is psychologic.

Tiredness results in decrease of energy, in lessened ability to receive sensory impressions from the outer world and in decrease in the will to do and to form decisions. Consciousness results from mental energy; hence tiredness interferes with all forms of activity of consciousness. Mental energy is a part of the vital process. It becomes exhausted with tiredness, and is restored in sleep. Physical labor also consumes energy. The central nervous system is the place where latent energy is converted into creative mental energy. The conversion of mental energy into nervous expressions and activities must bring about a physicochemical change. The effort to overcome tiredness or to keep awake may become painful. Sleep brings rest and a restoration of energy. The physicochemical changes which bring on tiredness become adjusted during sleep. The calcium content of the blood is lowered during sleep, and it is to be assumed that then the calcium, potassium and magnesium cations pass back again into the protoplasm of the muscles and nerve cells and by this means there develops an accumulation of potential energy of the neuromuscular system.

The feeling of tiredness is not controlled exclusively by physicochemical changes; it is influenced also by mental activity. The degree of attention is an important factor.

BERNIS, Rochester, N. Y.

Neuropathology

PATHOLOGIC EXAMINATION IN A CASE OF POSTVACCINAL ENCEPHALITIS IN WHICH RECOVERY OCCURRED. BERND HERKENRATH, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:293 (March) 1935.

Herkenrath makes the only report in the literature of a pathologic study in a postvaccinal encephalitis in which recovery took place. A girl, aged 3 years, was vaccinated after a previous unsuccessful vaccination about seven months before. There was a history of a convulsion at the age of 2 years and chickenpox about one month before. Six days after vaccination the child became febrile, vomited and had a convulsion, which was more marked on the left side. The next morning she had hemiplegia on the left side. She was drowsy, had spastic hemiplegia on the left side and reacted poorly to pinpricks on that side of the body. There were no signs of involvement of the meninges; there was a Babinski sign on the left; there were no differences in the tendon reflexes; the abdominal reflexes were diminished on the left. Lumbar puncture yielded fluid under a pressure of 160 mm. of water, containing 10 cells per cubic millimeter, and 72 mg. of sugar per hundred cubic centimeters. The Pandy and Nonne-Apelt tests gave negative results. On the third day the child had a morbilliform exanthem on the

palms and soles. A number of focal convulsive seizures occurred on the left side during the course of the disease, and on one occasion a seizure occurred in the right upper limb. The child's condition improved progressively. Neurologic examination twenty-five days after admission to the hospital showed no positive neurologic signs and no changes in the mental status. The child was discharged as recovered fifty-five days after admission. Three months later she was reexamined. Relatives reported that she was somewhat irritable. Neurologic and mental examinations gave negative results except for inability to speak as clearly as before the encephalitis.

Sixteen months after discharge the child was readmitted to the hospital with Vincent's angina. At this time neuropsychiatric examination gave negative results. The irritability and speech defect were no longer present. About one and one-half years after discharge the patient died of an intercurrent infection.

Examination of the internal organs revealed no significant findings. Grossly the brain was normal. Careful microscopic examination, utilizing all modern technics, showed only some fat-laden scavenger cells in the perivascular spaces of the cerebellum, pons, medulla and spinal cord. Most of these cells were small and round. These gitter cells were especially frequent in the venous perivascular sheaths. There was no evidence of perivascular, subependymal or cortical gliosis. There were no changes in the myelin sheaths. No alterations were present in the ganglion cells, except in the temporal lobes and in the right lateral nucleus of the thalamus, where there was a relatively marked atrophy of cells with diffuse increase of the smaller glia cells.

The only pathologic evidence, therefore, of the previous condition of the brain was the presence of perivascular gitter cells. There were no other perceptible residual signs of the severe infectious disease of the nervous system. The neural parenchyma was intact. Herkenrath refuses to consider the local tissue changes in the temporal lobes and in the lateral nucleus of the thalamus as sequelae of the encephalitic process. In addition to the unusual localization of these tissue changes for postvaccinal encephalitis, he notes the relatively frequent finding of such changes in the brains of children as a result of focal functional vascular changes. The conclusion is therefore warranted that there may be not only complete clinical recovery but also anatomic restitutio ad integrum.

SAVITSKY, New York.

WERNICKE'S POLIOENCEPHALITIS AS A MANIFESTATION OF CEREBROVASCULAR SYPHILIS. Y. UCHIMURA and H. AKIMOTO, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:685 (May) 1935.

Uchimura and Akimoto report a case of cerebrovascular syphilis accompanied by superior polioencephalitis. A mentally retarded Japanese housewife, aged 28, gave no definite history of venereal disease and no history of excessive use of alcohol. For ten years she had been suffering with progressive weakness of the muscles of the upper limbs and shoulder girdle, which was diagnosed in June 1929 as progressive muscular dystrophy. After a series of convulsions in the latter half of June 1929, she began to complain of headache and insomnia. She also showed changes in her mental status which required confinement in a psychopathic hospital. The mental picture was one of restlessness with confusion and recurrent periods of excitement and of abnormal behavior. Polyphagia and polydipsia were present. Neurologic examination showed pseudohypertrophic muscular dystrophy with tendon areflexia. The Wassermann reaction of the blood was positive, and that of the spinal fluid was negative; the colloidal gold test gave a syphilitic curve and the amount of globulin was increased.

Microscopic examination showed diffuse disease of the ganglion cells in the three upper layers of the cortex, with marked disorder of the cortical architectonics, so that all three layers at times seemed as one. The degenerated ganglion cells were replaced by numerous astrocytes and Hortega cells. Endarteritis of the smaller cortical vessels was present throughout the sections. Striking changes were found in the periventricular tissues, extending as far as the foramen of

Munro, though not beyond it. These alterations in the tissues were especially marked in the mamillary bodies. The pathologic picture presented by the periventricular changes was that seen in the cases of Wernicke's polioencephalitis. There were marked proliferation of the capillaries and precapillaries and diffuse endarteritic changes in the walls of the vessels. Progressive glial changes were present. Degeneration of the ganglion cells was present in the hypothalamic nuclei, with relative sparing of the supra-optic nucleus. The parenchymatous degeneration was most marked in the thalamus. There was some perivascular infiltration. The optic nerve and the chiasm showed marked gliosis. No perivascular infiltration was found. There were a few ring-shaped hemorrhagic areas in the periaqueductal gray matter and symmetrical changes in the dorsal nuclei of the vagus nerve that suggested polioencephalitis.

The parenchymatous degeneration in the cortex and in the periventricular region was secondary to vascular disease. Uchimura and Akimoto believe that the polioencephalitis was secondary to syphilitic endarteritis and that they were not dealing with two independent diseases. They conclude that syphilis can be the cause of Wernicke's polioencephalitis. They deny that the perivascular infiltration was due to a secondary infection, as has been maintained by Luthy and Walthard in other cases of Wernicke's polioencephalitis. No primary septic focus was found at autopsy. The authors suggest that the round cell infiltration in some cases may be a reaction to the parenchymatous degeneration. In this particular case it may be another manifestation of the syphilitic infection. They deny that there is any relation between the pathologic changes and the progressive muscular dystrophy.

SAVITSKY, New York.

THE RELATION BETWEEN PLASMOCYTES AND MICROGLIA CELLS IN TRYPANOSOMIASIS. E. WINKLER JR., Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:160 (June) 1935.

Winkler was able to study the relationship between plasmocytes and microglia cells in two cases of trypanosomiasis with a method, which he describes, in which both cells were stained adequately on the same slide. He found evidence of amniotic division of the nucleus in the plasma cells, with extrusion of part of this nuclear material. He was able to show many transitional forms between the plasma cells and the microglia cells. Some of the plasma cells showed protoplasmic processes resembling those usually seen in microglia cells. These cells showed the characteristic nucleus of the plasma cell, but at the same time structures were noted within the cell which stained like the Hortega cell. There were microglia with the characteristically elongated nuclei in which the protoplasmic processes stained like the plasma cell. None of the microglia cells showed division of the nuclei. The position of the very young Hortega cells was often near the plasma cell with the extruding nuclear material. When the plasma cells became less numerous the Hortega cells increased in number. The author concludes from this histologic data that in cases of trypanosomiasis most of the microglia cells come from plasmocytes.

SAVITSKY, New York.

Psychiatry and Psychopathology

INFLUENCE OF SIZE OF FAMILY UPON THE CHARACTERISTICS OF THE MENTALLY DEFICIENT. NEIL DAYTON, Am. J. Psychiat. **91**:799 (Jan.) 1935.

In a study of almost 21,000 retarded children in the public schools of Massachusetts, Dayton finds that the size of the family and certain other environmental factors exercise a significant influence on the personality characteristics of the subjects. While the average size of the family from which the defective children spring is about the same as that of the average family in the general population, higher intelligence quotients are general in smaller families. The differences were slight, but consistent. Only children in this group showed an average intelligence

quotient of 73, while those from families of ten or more children had an average intelligence quotient of 69. Only children showed reading accomplishment superior to those from large families, while the reverse was true of accomplishment in arithmetic. On the whole, small families provided better environmental conditions. Obedience and sociability were noted more frequently in children from large families, while seclusiveness and selfishness were more common in children from small families. Subjects in the latter group tended to show less suggestibility and quarrelsomeness than those from larger family units. Stealing and sex offenses were commoner in small families, and lying in large families. In general, the defective children from small families retained a greater degree of individuality and showed wider departures from the norm than those from large families.

DAVIDSON, Newark, N. J.

THE ETIOLOGY OF TEMPORARY AMNESIA. FREDERIC LEAVITT, Am. J. Psychiat. **91**:1079 (March) 1935.

Case histories of 104 patients suffering from temporary amnesia have been studied and are reported on by Leavitt. Three of the patients had aphasia rather than amnesia, and 8 were pure malingerers. These 11, however, are included in Leavitt's tabulation. The cause in about half of the cases was of an organic nature. Of these cases, in 3 the amnesia followed concussion, in 1 it followed a fracture of the skull, and in 11 it was associated with some toxic condition, notably alcoholism. There was also a case in which it was associated with renal toxicosis and diabetic hyperglycemia. In 10 instances the amnesia was classified as a postepileptic fugue. Of the patients in whom the condition was apparently not of a definite organic nature, 12 were psychoneurotic, 22 were psychotic, and 4 showed constitutional mental inferiority. Three of the patients in the last group were feebleminded. In 8 instances the etiologic factor could not be found. In the group of malingering and neurotic persons females predominated, but in the other groups most of the amnesic patients were males.

DAVIDSON, Newark, N. J.

RESEARCH IN PSYCHIATRY. H. DOUGLAS SINGER, J. A. M. A. **104**:2223 (June 22) 1935.

Singer stresses the importance of clinical research and discusses the relations that exist between clinical psychiatry and the two types of research included by Whitehorn and Zilboorg under the captions "psychologic" and "physiologic." Psychiatry is essentially a clinical subject. Advances in other fields of clinical medicine have led and not followed laboratory discoveries. It seems logical to conclude that this story will be repeated in psychiatry. There is still need of a continuation of the ancient methods of clinical observation, modified and elaborated to comply with advances already made. The author discusses briefly some of the forms of mental illness that are too often dealt with as if they were nosologic entities and also the group of psychoses labeled schizophrenia or dementia praecox. The occurrence of deterioration is today more or less ignored as a criterion for classification, and inclusion in the group depends on the observation of patterns of behavior that are characterized by excessive use of occult or highly symbolized responses, caricatures apparently of those features of human behavior which render social life possible—the repressive and substitutive types of reaction. One need not question the propriety of classifying psychologically such behavior in one class, but few will disagree with the remark that it is not a nosologic or a psychiatric unity. The situation is much the same in regard to the psychoneuroses. The author states that the methods of clinical research in psychiatry are no different in principle from those employed in other fields of medicine. He does not share the not uncommonly expressed opinion that psychiatry has graduated from the stage of description to that of interpretation. This may be true of psychology, but it is not true of psychiatry. It may be granted that there has been careful and adequate description of the superficial manifestations and spontaneous behavior.

What remains to be done concerns the devising of methods of recording the responses to controlled situations, planned with the purpose of defining exactly what integrated functions persist in any given case and what are lost or are in abeyance. This is a long, tedious road, requiring persistence, imagination and ingenuity, the usual tools of research, but it is, he believes, the only road that will lead to a successful classification on an etiologic basis and through this to adequate correlation with other fields of research. EDITOR'S ABSTRACT.

THE CONSTRUCTIVE ABILITY OF ONE HUNDRED AND FIFTY SUBNORMAL CHILDREN. EDNA WILLIS MCELWEE, J. Juvenile Research **19**:25 (Jan.) 1935.

The purpose of the study reported was to compare the constructive ability of several groups of retarded children, whose mental ages were nearly constant but whose chronological ages were variable. One hundred and fifty children were included in the study. Each child was examined by the Stanford-Binet test, and their constructive ability was also tested. The gain in constructive ability with physical maturity is apparent. These findings are substantiated by the results of a study made in Minnesota. FERGUSON, Niagara Falls, N. Y.

SYPHILIS AND MENTAL DISEASES. WILLIS E. MERRIMAN, J. Social Hyg. **21**:164 (April) 1935.

During the year ending June 1933, syphilis was considered a causative factor in the cases of 11.3 per cent of all new patients admitted to the civil state hospitals. In 1931 Pollock computed the annual economic loss resulting from mental disease due to syphilis in the state of New York as approximately $13,500,000. The incidence of dementia paralytica in that state is nearly three times as great in cities as in rural districts when the estimate is based on respective urban and rural populations. Of over 16,000 patients with dementia paralytica admitted to the state hospitals during two recent decades, 13,000 died within an average of less than two years following admission. Modern methods of treatment have proved to have a decided advantage over earlier ones, but apparent recoveries are secured only in a distinct minority of cases. FERGUSON, Niagara Falls, N. Y.

MENTAL DISEASE IN THE CRISIS. PAUL O. KOMORA and MARY A. CLARK, Ment. Hyg. **19**:289 (April) 1935.

Although there has been a rapid increase in the number of persons in state hospitals for patients with mental diseases since the beginning of the economic depression, it is not possible to conclude from this that the crisis has been a major etiologic factor in the augmented incidence of mental disease. More than half of the state hospitals in the country replied to the questionnaire of the National Committee for Mental Hygiene, and in these institutions there has been an increase of 15.5 per cent in the number of patients admitted for the first time in the triennium from 1929 to 1932. There has also been an increase in the number of paroles—almost 10 per cent—since 1929. The latter datum suggests that hospital officials, under the pressure of an increasing number of persons sent to the hospital, are redoubling efforts to release patients. The ratio of the population of the state hospitals to the general population increased from 207.5 per hundred thousand in 1923 to 254.8 ten years later. However, this increase may be ascribed to other factors, such as (1) an increase in the number of state hospitals available, (2) the growing tendency of the population to use hospitals for all sorts of illnesses, (3) improvement in the type of care offered to the patient and the constant increasing readiness of the public to use such facilities, and (4) the transfer of many patients from private to state institutions because of the poverty of the family. Since mental illness must be thought of as the end-result of a chain of causes, it is unlikely that any psychoses actually produced by the economic crisis would be reported as yet. DAVIDSON, Newark, N. J.

THE EFFECT OF INTERCURRENT SOMATIC DISEASE ON MANIC-DEPRESSIVE REACTIONS. LEWIS R. WOLBERG, Psychiatric Quart. **9**:88 (Jan.) 1935.

Six cases of manic-depressive psychosis in which intercurrent somatic disease precipitated recovery are reported. In one case recovery followed perineorrhaphy and surgical amputation of the cervix; in two instances the somatic disease was a carbuncle, and in two others a localized infection of the foot was the provoking agency. In the last case a peritonsillar abscess preceded recovery. In four cases hyperpyrexia occurred; in one moderate fever developed; in the case in which operative measures were employed the temperature is not reported. Wolberg considers the somatic disease a form of shock therapy. He suggests that psychotic patients have been emotionally and psychically sensitized and construes the somatic disease as a desensitizing agency of nonspecific nature.

DAVIDSON, Newark, N. J.

EXCERPT FROM THE ANALYSIS OF A DOG PHOBIA. EDITH STERBA, Psychoanalyt. Quart. **4**:135, 1935.

Sterba points out first that an animal phobia is produced by the displacement onto an animal of the child's libidinal and aggressive feelings about some adult important in the child's emotional life. The case she reports not only reveals a number of mechanisms in the development and avoidance of anxiety in the female child but illustrates the conversion of the animal phobia into another type of neurosis.

The dog phobia of Sterba's patient, a girl, was based on the fear that a dog might bite her as a punishment for masturbation. This resulted from the chronological association of the mother's stern prohibition of masturbation ("You will make yourself sick" or "I will send you away") and the father's command not to put her hand in a dog's mouth, as she was doing, lest he bite her; i. e., there was actually a possibility that the hand she had used to masturbate might be injured by the dog. On a deeper level, she feared that the dog might smell at and injure her anus. The dog was a substitute for her father, who might injure her if he had intercourse with her as he had with her mother. It was also a substitute for her mother, who had given her libidinal pleasure through the many enemas she had administered during the child's attack of measles just before her illness began. The wish to keep her back turned to the dog was an expression of her anxious defense against a passive anal surrender first to the father, with whom such a passive anal attitude was bound up with the idea of a severe physical injury, and, second, to the mother on account of the enemas. The dog phobia was a converted expression of longing for a repetition of these enemas from her mother. From this it is evident that the libido at the beginning of the illness was attached chiefly to the anal-sadistic level of organization. The rapid disappearance of the dog phobia after two months' analysis occurred because the mother's prohibition against playing at giving enemas was too much bound up with the real mother and not with a super-ego requirement, so that the analyst's permission to play at this game was more easily accepted. Behind the conflict over the desire to play at giving enemas lay the overstrict training in cleanliness to which she had been subjected. Another reason for the rapid disappearance of the dog phobia lay in the ease with which she assumed the aggressive masculine rôle—to give the enemas, to be a boy and to talk like a boy—as a further defense against her passive feminine desires. The change from the dog phobia to the obsessional symptoms came about during the summer when analysis was interrupted by a vacation. The patient was alone with the mother, who again increased her fears by forbidding her anew to play the enema game with her sister and by adding a new threat that if she did so she would be sent away. These disappointments aroused a storm of violent aggression against the mother and caused the child to wish the mother's death. But the threat of withdrawal of love forced the child to turn these aggressive impulses against herself,

and the obsessional neurosis resulted. When these aggressive impulses toward the mother were made conscious and expressed in play and dreams, the neurotic symptoms based on the suppression of the hostility were removed.

PEARSON, Philadelphia.

THE AFTER-RESULTS OF PSYCHOTHERAPY IN FIVE HUNDRED ADULT CASES. MARY C. LUFF, Brit. M. J. **2**:55 (July 13) 1935.

The results of psychotherapy in 500 consecutive adult patients who attended the Institute of Medical Psychology are analyzed. Sixty-five and five-tenths per cent of the patients were much improved or improved on completion of the treatment. Follow-up studies after three years reduced this to 55 per cent. Analysis based on length of treatment showed that one half of the patients were treated for a short period. This implies that the patient had less than twenty interviews. Ten per cent made more than sixty visits, while the remaining group were seen between twenty and sixty times. The results in all three groups were almost identical. The most satisfactory results were effected in patients who had anxiety reactions or who complained of sexual maladjustments.

BECK, Buffalo.

AN INVESTIGATION INTO THE AFTER-HISTORIES OF DISCHARGED MENTAL PATIENTS. L. H. WOOTON, R. W. ARMSTRONG and DOROTHY LILLEY, J. Ment. Sc. **81**:168 (Jan.) 1935.

A follow-up study was made of persons who left a small hospital for patients with mental diseases in London during the period from 1928 to 1932. A competent psychiatric social worker studied the patients from the point of view of mental health, number of recurrences and environment. Most of the patients had schizophrenia. The results do not support the conventional opinion of the outlook in cases of schizophrenia. A study of thirty-eight patients showed that eighteen, or nearly 50 per cent, had remained well since discharge. The percentage of relapses rose sharply during the first three months after discharge, probably because of the number of persons who were prematurely discharged, owing either to the insistence of relatives or to poor judgment of the members of the medical staff. The next peak occurred at about the end of the first year, when there appears to be a maximum tendency to relapse for which Wootton and his co-workers are unable to account. They postulate that treatment in a hospital for patients with mental diseases succeeds in many cases in obtaining a type of recovery which lasts approximately a year and that this is a critical period. Once this period is passed, the tendency to relapse gradually diminishes. In cases of schizophrenia there is another danger period toward the end of the second year. The importance of pregnancy or the puerperium as a precipitating factor is questioned by the authors. They believe that an isolated psychotic attack carries with it in many cases a latent tendency to recurrence.

KASANIN, Chicago.

THE ASSOCIATION OF PHYSIQUE AND MENTAL CONDITION. J. L. CLEGG, J. Ment. Sc. **81**:297 (April) 1935.

One hundred men with schizophrenia, 100 with manic-depressive psychosis and 100 normal men were examined anthropometrically to determine the correlation of body build and mental disease. In all three groups the subjects were selected at random between the ages of 25 and 55. All subjects with any physical deformity were excluded.

It was found that the stature and cranial capacity of the psychotic persons were less than those of the normal subjects. This was probably due to a diminution in the length of the head and in the height. The faces of the psychotic subjects were narrower than those of the normal subjects, the narrowness being especially prominent in the lower part of the faces of the persons with schizophrenia. The faces of the subjects with manic-depressive psychosis were shorter

and more shield-shaped than those of the subjects with schizophrenia. The noses of the psychotic subjects tended to be longer than those of the normal subjects; those of the schizophrenic subjects were also narrower. The persons with schizophrenia had shorter upper lips than the persons in either of the other two groups. The arms were shorter in the psychotic than in the nonpsychotic persons; this was especially noticeable in the group with schizophrenia. Increased pelvic width was common in the persons with manic-depressive psychosis. The shoulders were narrower and the neck was shorter in the psychotic than in the nonpsychotic group.

KASANIN, Chicago.

THE INTER-RELATIONSHIPS OF MENTAL DISORDERS AND DIABETES MELLITUS. WILLIAM C. MENNINGER, J. Ment. Sc. **81**:332 (April) 1935.

The relationship between mental disorders and diabetes was studied in 30 cases of diabetes associated with a psychosis, in 93 cases of uncomplicated diabetes and in 400 cases of mental disorder, which apparently served as controls for the study. Menninger believes that certain fluctuations of a specific type occur with sufficient frequency in diabetic persons to suggest a picture descriptive of the diabetic personality. These are not obvious to the internist. Long periods of study show mild but definite disturbance in the fields of perception, emotion and volition and in the intellectual functions. A small percentage of cases are definitely instances of toxic psychosis or true "diabetic psychosis." Psychologic conflicts may be an important etiologic factor in many cases of diabetes. Menninger goes further when he states that although he has no definite proof, he thinks that such conflicts may even cause diabetes.

Gross psychologic trauma may initiate diabetes, although the real causes are usually unconscious conflicts, with absence of any external event or situation. Mental disorder and diabetes never occur independently in the same person.

KASANIN, Chicago.

ACHLORHYDRIA IN THE PSYCHOSES WITH SPECIAL REFERENCE TO COINCIDENT ANAEMIA. RUBY O. STERN, J. Ment. Sc. **81**:358 (April) 1935.

Three hundred psychotic patients were studied to determine the incidence of achlorhydria as compared with that in normal persons. Achlorhydria was present in 10.6 per cent of the psychotic patients. This was 4 per cent lower than the occurrence among large numbers of healthy people in the same age group. Stern concludes that achlorhydria does not occur more frequently in psychotic patients. There is no association between achlorhydria and psychoses.

KASANIN, Chicago.

THE SYNDROME OF NEUROTIC ANXIETY: THE SOMATIC AND PSYCHIC COMPONENTS OF ITS GENESIS AND THERAPY. WALTER MISCH, J. Ment. Sc. **81**:389 (April) 1935.

Misch studied fifty cases of true anxiety. The somatic syndrome of anxiety is characterized by a stormy excitation of the sympathetic nervous system. At first one finds an exclusive excitation of this system, but toward the end of the attack phenomena referable to the parasympathetic system are added. The symptoms are those of intense vasoconstriction of the skin with paresthesias, sensations of cold, pallor, tachycardia, dryness of the mouth, cold sweats, mydriasis, hypertension and relaxation of the voluntary muscles.

Misch has attempted to treat anxiety as a somatic disease. A search was made for a drug that would dilate the peripheral vessels, slow the heart rate, lower the blood pressure, stimulate salivary secretion, dilate the pupil and increase muscle tone. Such a drug was found in the choline preparations. After intramuscular injection of 0.1 cc. of acetylcholine hydrochloride in cases of acute anxiety, in from five to ten minutes there were ample flow of blood through the skin, diminution of tachycardia and disappearance of subjective phenomena. At the same time the

physical symptoms of the anxiety state disappeared and were followed by a feeling of comfort and well being. The effect of the drug lasted from three to four hours.

Choline was administered orally. In the majority of cases, within from a few hours to two days after the commencement of the treatment there was gradual improvement, which in a short time led to complete freedom from anxiety. Permanent improvement was observed in some cases; in others the symptoms reappeared in a milder form, to disappear again after more treatment. In the patients treated by choline all forms of psychotherapy were avoided. Choline was always effective in cases of pure anxiety, especially in the forms in which the patients had not yet undergone strong psychic fixation. It was only conditionally effective in cases of anxiety hysteria. It was of no value in cases of anxiety of the compulsion neuroses type, in cases of psychotic anxiety, in cases of anxiety caused by hypnosis or in cases of posthypnotic phobia. Choline preparations exercise their maximal action on the parasympathetic system in akinetic anxiety syndromes. The effect of choline is greater the more elementary the form of the anxiety; its effect is less definite in cases in which the anxiety has been psychically elaborated.

KASANIN, Chicago.

INSTINCT DUALITY IN THE DREAM. LUDWIG JAEKELS and EDMUND BERGLER, Imago **20**:393, 1934.

Freud's hypothesis of the death instinct has not gained the universal acceptance of psychoanalysts and has been subject to attack, especially by Reich. Jaekels and Bergler, however, accept the hypothesis and attempt in this article to show the manifestations of the death instinct in the dream. Sleep has been frequently related to death, especially in the literature and in mythology. One aspect of sleep is related to dying, and thus the dream in part serves the purpose of hampering too deep a sleep as a defense against death. Freud's original conception of the dream as a wish fulfilment holds true for id wishes of repressed infantile sexuality. Since the super-ego is genetically related to the internalization of aggression (death instinct drives), manifestations of it in dreams have been taken by the authors as evidence of expression of the death instinct. The dream, then, has two functions: (1) to deny the temporarily present unconscious reproach of the super-ego and (2) to satisfy a repressed infantile id wish. The first of these functions represents a hitherto unnoted aspect of the dream.

KAUFMAN, Cambridge, Mass.

Diseases of the Brain

SIMULATION OF INTRACRANIAL TUMOR BY LEAD ENCEPHALOPATHY IN CHILDREN, WITH REMARKS CONCERNING SURGICAL TREATMENT OF LATTER. PAUL C. BUCY and DOUGLAS N. BUCHANAN, J. A. M. A. **105**:244 (July 27) 1935.

Bucy and Buchanan performed suboccipital decompression in two of three cases of lead encephalopathy in children with increased intracranial tension which simulated cases of intracranial tumor. Both children recovered promptly and completely. In the third case, in which the intracranial pressure was less elevated, no decompression was carried out and medical management alone was used. The child had a prolonged and stormy course but also ultimately recovered. From these experiences and from data taken from the literature, it is concluded that the differentiation of lead encephalopathy and midline cerebellar tumors in children from the history and physical signs alone is difficult and may be impossible. Such factors as the possible ingestion of lead, rapid onset with vomiting and abdominal pain and only moderately increased intracranial pressure should warn the clinician of the possible diagnosis of lead encephalopathy. The easiest and most rapid method of rendering probable the diagnosis of lead encephalopathy is the demonstration of the presence of lines of increased density at the ends of the long bones.

The diagnosis may then be established by demonstrating the presence of lead in the blood. Medical management of lead encephalopathy is notoriously unsatisfactory and results in a high mortality and numerous and serious sequelae. Surgical decompression of the intracranial cavity offers a logical means of producing a prompt and complete relief of symptoms with less danger of sequelae.

EDITOR'S ABSTRACT.

THE PHYSIOLOGY, PATHOLOGY AND TREATMENT OF CRANIOCEREBRAL INJURIES. WINCHELL M. CRAIG, New England J. Med. **212**:777, 1935.

The pathologic and the physiologic course of a craniocerebral injury depend not only on the severity of the trauma but also on the extent of the lesion and the type of treatment which is administered. In 80 per cent of the cases such an injury is followed by posttraumatic symptoms. The mortality is 25 per cent. Posttraumatic edema probably plays a larger part in the production of symptoms than does laceration of the brain or hemorrhage. A roentgenogram does not always disclose the extent of injury. Injuries to the meninges and to the cerebral cortex are usually missed unless further studies are carried out. Prolonged rest in bed is the best procedure to abort possible after-effects, and frequent observations of the blood pressure and the pulse and respiratory rates over a long period are advisable. The production of cerebral edema is associated with concussion of a greater or lesser degree. The exact explanation of edema is uncertain, but it is known that it occurs when there is an increase of colloids in the tissue. Contusion of the brain usually indicates localized injury to the cerebrum, and its symptoms develop after a latent period, which is in distinct contrast to concussion, the symptoms of which are immediately apparent. Contrecoup injury in contusion occurs at the opposite pole of the skull and may be more serious than that occurring at the site of the trauma.

MOORE, Boston.

SOME CLINICAL MANIFESTATIONS OF TRAUMATIC DECEREBRATION. AARON J. ROSANOFF, Psychiatric Quart. **9**:116 (Jan.) 1935.

The phenomena of decerebrate rigidity occasionally occur in human beings as a result of cerebral trauma. This is especially true of injuries at birth; thus, trauma at birth is much more likely to precipitate epilepsy than is injury to the head in later life. The brain is better able to tolerate compression than extension. In the process of molding the head at birth the decerebrating lesion is probably produced more by the forces along the vertical axis and subsequent compensatory extension than by the compressing forces applied along the transverse diameters of the skull. At any time prior to the closure of the fontanels, injury to the head is likely to provoke extension of the brain tissue. In the adult, on the other hand, a traumatic decerebrating lesion can scarcely be produced except by extensive localized destruction of brain substance.

Since it is true that in most cases of mental deficiency, Little's disease and epilepsy no trauma at birth is reported, it is clear that there is a factor of vulnerability as well as one of trauma. The degree of vulnerability depends on and varies with factors such as hereditary disposition, sex (males are more vulnerable), maturity at birth and multiplicity of pregnancies. Among surviving premature children there is a higher incidence of Little's disease, epilepsy and mental deficiency than among maturely born infants. A similar variation is found among twins. Mental deficiency, mental disease, criminality, epilepsy and similar conditions occur more often among the first born than among the later born. The greater hazard of trauma at birth among the first born is suggested as an explanation.

In explaining the frequency with which a long silent period occurs between an injury to the head and the onset of a convulsive disorder, Rosanoff is inclined to accept the hypothesis of Foerster and Penfield. This holds that cicatricial traction, by producing a spreading reflex vasomotor spasm, starts the seizure. The slowly

developing neuropathologic changes which may be at work in the interval between the injury and the first clinical evidence include dilatation and distortion of the ventricles and the formation of cysts, atrophies, adhesions, neuroglial overgrowths, scleroses and cicatrices.

DAVIDSON, Newark, N. J.

COLLOID CYST OF THIRD VENTRICLE OF THE BRAIN: REPORT OF A CASE OPERATED ON, WITH RECOVERY. J. E. PATERSON and M. LESLIE, Brit. M. J. **1**:920 (May 4) 1935.

A patient aged 34 had intermittent attacks of headache, with the intervals of freedom from pain gradually shortened. Ventriculography demonstrated pronounced hydrocephalus of the lateral ventricles with absence of visualization of the third ventricle. Neither ventriculography nor injection of dye showed any abnormality. A cyst of the third ventricle was found at operation, after which the patient made an excellent recovery except for two epileptiform seizures.

The authors emphasize that perforation of the septum lucidum is not uncommon with prolonged hydrocephalus, and they warn against the ease of making a fallacious diagnosis when this occurs.

BECK, Buffalo.

BLOOD VESSEL TUMOURS OF THE BRAIN WITH PARTICULAR REFERENCE TO THE LINDAU SYNDROME. G. S. HALL, J. Neurol. & Psychopath. **15**:305 (April) 1935.

An interesting case is reported to illustrate the relationship between an angiomatous malformation and hemangioblastoma. The angiomatous malformation is essentially a benign, nonfamilial tumor, which rarely gives rise to cystic formation. It is not associated with any visceral anomalies but is often accompanied with congenital nevi of the skin and occurs most commonly in the cerebral hemispheres. The hemangioblastoma is a true tumor formation and is frequently cystic. It occurs chiefly in the cerebellum. It may be familial and is unaccompanied by any lesion of the skin; it may be associated with visceral anomalies and angiomatous retinas. In the case reported here the growth was a multiloculated cystic tumor in the left cerebellopontile angle, associated with angiomatosis of the central portion of the retina and with an extensive capillary nevus over the upper part of the thoracic and the cervical region.

SPERLING, Philadelphia.

POSTURAL HYPOTENSION. W. F. CROLL and R. J. DUTHIE, Lancet **1**:194 (Jan. 26) 1935.

Croll and Duthie report their observations on a man, aged 37, in whom a marked fall of blood pressure, accompanied by dizziness, invariably took place when he changed from the supine to the standing position. The heart was normal in size and position, and the sounds were normal. An electrocardiogram showed preponderance of the left side. A pseudo-Argyll Robertson pupil was present on the left, and absence of knee jerks was noted. Serologic tests of the blood gave normal results. The fall of blood pressure was associated with a marked decrease in the excretory function of the kidneys. When given 100 cc. of water to drink while lying down, the patient passed 880 cc. of urine, with a specific gravity of 1.003, in the next four hours. When the experiment was repeated on the following day, but with the patient up and moving about, he passed only 73 cc. of urine with a specific gravity of 1.014. The pulse rate showed a normal response to change in position. Abdominal compression, the application of tourniquets around the limbs and the administration of epinephrine, solution of pituitary and histamine all failed to prevent the fall in blood pressure.

Langworthy has pointed out that the predominant afferent impulses responsible for the control of postural tone are proprioceptive and arise in the muscles of the extremities. It is the opinion of Croll and Duthie that there was a possible derangement of the nervous mechanism controlling the blood pressure in their

case. The knee jerks were absent, and as there were no signs of a defect of the anterior horn cells or of the efferent nerves controlling the reflex, they concluded that afferent fibers from the muscles were defective and that possible proprioceptive fibers controlling changes of blood pressure were implicated.

WATTS, Washington, D. C.

FACIOCRANIAL DYSOSTOSIS (CROUZON'S DISEASE) IN A HEALTHY FAMILY. P. BURTON and AUGUST O. LEY, J. belge de neurol. et de psychiat. **35**:57 (Feb.) 1935.

Burton and Ley present the case of a patient with Crouzon's disease, the important features of which they describe as (1) cranial deformity similar to oxycephalia; (2) malformation of the face with flattening of the nose and superior micrognathia giving way to inferior prognathia, and (3) ocular difficulties, such as atrophy of the optic nerve, exophthalmos and divergent strabismus. Although the syndrome is considered familial and hereditary, it may be seen as an isolated condition. The case reported is that of a child, aged 3½ years, who at the age of 3 months had hydrocephalus with exophthalmos and strabismus but no atrophy of the optic nerve. There was at that time a fairly typical facial expression. The family and developmental history is without significance except for delay in walking. A roentgenogram showed the bones of the skull to be thin, with symmetrical deformities on both sides, with visible fontanels, a rather opaque cerebral vault, small maxillary sinuses and normal dentition. The vestibular apparatus was not stimulated by caloric tests. A lumbar puncture revealed high pressure. The fluid was normal. At the age of 3½ years, the intelligence quotient was rated as between 18 months and 2 years.

WAGGONER, Ann Arbor, Mich.

BRADYCARDIA IN CASES OF TUMOR AND OF ABSCESS OF THE BRAIN. J. RASDOLSKY, Deutsche Ztschr. f. Nervenh. **137**:126 (June) 1935.

Bradycardia has long been considered one of the most important and frequent symptoms in cases of tumor of the brain. Rasdolsky, on the basis of his experience, emphatically denies this. In 234 cases of tumor of the brain he found only seven, or 3 per cent, in which there was spontaneous bradycardia. Of the 234 cases, he records headaches in 82 per cent, choked disks in 68 per cent, vomiting in 59 per cent and epileptic attacks in 18 per cent. Bradycardia, therefore, can scarcely be considered a frequent and important symptom in cases of tumor of the brain. In cases of abscess of the brain, on the other hand, the author found bradycardia to be a frequent symptom. He found it in 75 per cent of forty-five cases. These findings lead him to suggest that when bradycardia is present one must think first of abscess of the brain and only after excluding this diagnosis can one consider tumor of the brain.

As to the mechanical cause of bradycardia in cases of tumor of the brain, Oppenheim expressed the opinion that it is due to stimulation of the vagus nerve in the medulla, caused either by general or by localized pressure. Rasdolsky cannot accept this opinion. In the seven cases of tumor of the brain with bradycardia the growth was localized in the posterior fossa in only three. Apparently other factors must also play an important part. Rasdolsky found that the development of bradycardia was due chiefly to a rapid increase in intracranial pressure. All seven patients died with signs of a rapid increase in intracranial pressure.

To substantiate this contention, the author calls attention to the following: 1. In cases of increased intracranial pressure, bradycardia may appear temporarily as a result of coughing, pressure or bodily exertion. The acute increase in intracranial pressure is accompanied by an increase in the severity of the headache and by vomiting, dizziness, stupor or loss of consciousness. 2. Ordinary bradycardia develops as a result of herniation of the cerebellum or tumor into the occipital foramen. The author observed three such cases. 3. Bradycardia may also develop

following lumbar puncture in the presence of increased pressure. Three of the author's patients died from three and one-half to five hours after a lumbar puncture. 4. Bradycardia is observed in cases of hemorrhage of the middle meningeal artery and of edema of the brain resulting from trauma; such conditions cause a sudden increase in intracranial pressure.

In cases of abscess of the brain intracranial pressure develops rapidly, and the author thinks that this fact accounts for the presence of bradycardia in such cases. That toxic processes may be responsible for the bradycardia in cases of abscess of the brain is less likely.

BERNIS, Rochester, N. Y.

POSTURAL DISTURBANCES AND THE ABILITY TO INFLUENCE THEM: A CLINICAL STUDY OF PATIENTS WITH MOBILE SPASTIC TORTICOLLIS. F. QUADFASEL and H. KRAYENBÜHL, Monatschr. f. Psychiat. u. Neurol. **88**:39 (Feb.) 1934.

The results of a study of twenty-three cases of mobile spastic torticollis are reported. Most of the patients were observed for many years. The illness usually begins insidiously and may last for decades. The patients do not possess hysterical types of personality. In cases in which there is a favorable outcome, recovery is gradual. A considerable number of patients presented symptoms of an organic character, such as inequality of reflexes, myoclonic twitchings or spasms and involuntary turning movements of different parts of the body. Evidence of encephalitis as an etiologic factor was seldom observed. In six cases the symptoms had disappeared completely after an illness lasting from eight months to two and a half years. Marked improvement was noted in four cases, the only residual symptom being continuous fine tremors of the head. It was found that the torticollis could be influenced by a variety of measures, including changes of posture of different parts of the body and sensory stimuli. These influences belong in the group of phenomena described by Goldstein as induced tonic changes. Nine patients were given atropine sulfate, and five showed definite improvement. Quadfasel and Krayenbühl are of the opinion that spasmodic torticollis is an organic disorder. An analysis of their observations showed that influences which help in the attainment of normal posture exert a favorable effect on the symptoms. The disorder is a result of a disturbance in the symmetrical action of stimuli and the attempt of the body to maintain a normal posture. Tremors and shaking movements are an expression of the unresolved struggle between the disturbance and the attempt at postural regulation.

ROTHSCHILD, Foxborough, Mass.

TESTS FOR HEPATIC FUNCTION IN CASES OF MULTIPLE SCLEROSIS. K. HAUG, Monatschr. f. Psychiat. u. Neurol. **88**:225 (April) 1934.

Using the galactose tolerance test and the aldehyde test for the determination of urobilinogen in the urine, Haug studied the functional activity of the liver in fourteen cases of multiple sclerosis. Of twelve patients who were not receiving any medication, seven showed a decreased tolerance for galactose and five a weakly positive reaction for urobilinogen. Advanced neurologic changes were observed in all cases in which abnormal results were obtained, but equally severe involvement of the nervous system was noted in some of the other cases. Two patients who were receiving morphine showed pronounced disturbances of hepatic function. Three patients were given paraldehyde and barbital for prolonged periods, but later tests failed to disclose any alterations. The prolonged administration of liver preparations and decholin to patients presenting disturbances in the functional activity of the liver led to an increase in the tolerance for galactose and a decrease in the urobilinogen content of the urine. Slight clinical improvement occurred in some of the cases. Haug is of the opinion that the abnormalities of hepatic function disclosed by his studies are not primary but are an expression of involvement of the central nervous system by the disease process.

ROTHSCHILD, Foxborough, Mass.

THE RELATIONSHIP BETWEEN FATAL EPILEPTIC SEIZURES AND METEOROLOGICAL CONDITIONS. IRENE BRUCKMÜLLER, Ztschr. f. d. ges. Neurol. u. Psychiat. **151**:691 (Dec.) 1934.

Fifty-one patients with essential epilepsy uncomplicated by other general diseases were studied in relation to the beginning of the fatal epileptic seizures and atmospheric conditions. Twenty-seven of the seizures occurred with cold and ten with warm winds. It is believed that there is a definite relationship between the fatal attack and the atmospheric changes, especially cold winds, and that meteorological factors play a rôle in precipitating nonfatal epileptic attacks.

MICHAELS, Boston.

Diseases of the Spinal Cord

TRIPLEGIA FOLLOWING TONSILLECTOMY. A. BERNARD BRAHDY, Am. J. Dis. Child. **49**:716 (March) 1935.

The case is reported of a boy, aged 7 years, in whom five days after tonsillectomy there developed, in a rather short period, flaccid paralysis of both lower extremities and of the right upper extremity. This was accompanied by complete loss of sensation to the level of the seventh thoracic segment on the left, with one segment of hyperesthesia on the left and involvement of all cervical segments on the right; there were also distention of the abdomen and incontinence of urine. Lumbar puncture revealed xanthochromic fluid, with 590 cells, which were mostly crenated red cells. Manometric tests gave normal results. Two weeks after admission the patient had an attack during which he became lethargic and irrational; this was followed several hours later by edema of the face, legs and ankles. The patient vomited blood and there was bright red blood in the stools and in the urine. Two days later the symptoms began to disappear, and at the time of discharge there was improvement in the condition of the right upper extremity. Three and one-half years later the patient had recovered use of the upper extremity, but he still had complete anesthesia and flaccid paralysis below the sixth thoracic segment. Brahdy believes that the condition was due to at least two emboli cutting off the blood supply to the spinal cord.

WAGGONER, Ann Arbor, Mich.

POLIOMYELITIS: A STUDY OF FOUR HUNDRED AND TEN PATIENTS AT THE PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES. PASCAL F. LUCCHESI, Am. J. M. Sc. **188**:515, 1934.

In 1932 Philadelphia experienced its second epidemic of poliomyelitis; during the summer and fall 410 patients admitted to the Philadelphia Hospital were suspected of having acute anterior poliomyelitis. The diagnosis was verified in 304 (74.1 per cent). The diagnosis of poliomyelitis was made only when the patient presented the accepted clinical and pathologic picture. Positive findings in the spinal fluid were obtained in most cases. No diagnoses of abortive poliomyelitis were made, the patients being discharged with a diagnosis of poliomyelitis with or without paralysis.

Two hundred and fifty-four patients (83.5 per cent) received serum; 124 of these showed weakness or paralysis on admission. On discharge from the hospital this number had increased to 154. Fifty patients (16.5 per cent) received no serum on admission. Of this number 28 showed weakness or paralysis. On discharge this number had increased to 38. One hundred and ninety-two (63.2 per cent) of the patients were discharged with evidence of paralysis, whereas on admission 152 (50 per cent) presented such evidence. There were 24 deaths (7.89 per cent), 18 of the patients having received serum. Seventeen of the patients who died required the use of the respirator, and 10 died in the respirator.

In view of these findings, Lucchesi says that the conclusion seems justified that the convalescent serum was of little value in the prevention of paralysis.

WATTS, Washington, D. C.

BLOOD VESSEL TUMOR OF THE SPINAL CORD IN A BOY AGED NINE YEARS WITH ESPECIAL REFERENCE TO A NEW DIAGNOSTIC SYNDROME. WILLIAM C. BLACK and HAROLD K. FABER, J. A. M. A. **104**:1889 (May 25) 1935.

Black and Faber cite a case of intradural venous tumor, probably a hemangioendothelioma, with associated varices, in a boy aged 9 years. Froin's syndrome was present. The reaction to the Queckenstedt test was negative, but it became positive after the withdrawal of spinal fluid below the level of the lesion. On the injection of iodized poppy-seed oil 40 per cent, the peculiar distribution of the oil in droplets suggested that it might be pathognomonic of subarachnoid varices and vascular tumors of the spinal cord large enough to obstruct the subarachnoid space. It was apparent to the authors that in their case there was a unique combination of changes in the spinal fluid. The conjunction of the Froin syndrome with a negative reaction to the Queckenstedt test which becomes positive when the lumbar sac is drained of a relatively small amount of fluid could probably not be produced by any type of lesion other than the one under consideration. The vascular tumor, whether composed of varices or of smaller vessels, transmits pressure from the subarachnoid space above to the lumbar sac below, thus acting essentially as a column of liquid, even though there is no direct communication between the two. However, when the fluid is drawn off below and the tumor sags down under the unopposed pressure from above, the attachments of the tumor are drawn tight, producing an obstruction in the spinal canal like that of a solid tumor and so causing the reaction to the Queckenstedt test to become positive. Worthy of special attention is the peculiar distribution of iodized oil in droplets over two or more segments. The progress of the case harmonizes with the view expressed by Sargent and Rand that operation (laminectomy) is of little or no permanent value. Globus and Doshay believe that operation affords some benefit as the result of decompression. The authors' patient was slightly improved after operation, but only for a short time. Spontaneous remissions, especially in cases of varices, have been repeatedly noted and may explain temporary improvement as well as does decompression. High voltage roentgen therapy was without detectable effect.

EDITOR'S ABSTRACT.

A STUDY OF SYRINGOMYELIA AND THE FORMATION OF CAVITIES IN THE SPINAL CORD. E. S. TAUBER and O. R. LANGWORTHY, J. Nerv. & Ment. Dis. **81**:245 (March) 1935.

Tauber and Langworthy declare that trauma occurs too often with symptoms of syringomyelia to be disregarded as a cause. Three cases from the Baltimore City Hospital are cited in which there were clinical signs of syringomyelia but a different causation. A study of the circulation of the spinal cord was undertaken, and the authors emphasized that the arteries in the upper part of the thoracic region are the smallest of those on the ventral surface and are of much less volume than those in the lower part of the thoracic region where cavities are less frequent. The importance of disturbances of the blood supply in the production of lesions in the spinal cord has not been given the emphasis that it merits. The authors consider that the theory of a congenital defect of glia cells has no proof, pathologic or experimental. Sudden degeneration of the white substance of the cord, as in cases of acute disseminated encephalomyelitis, has been followed by cavitation, illustrating what may happen when there is not time for glial proliferation to heal the necrotic area. Cavitation is likewise reported in association with tumors, thrombosis, syphilitic meningomyelitis, hematomyelia and concussion. It seems that the fifth cervical segment is the most vulnerable spot for anemia of the cord, since here there are two different sources of blood supply to the cord. The authors were able to produce cavities in the cord similar to those in cases of syringomyelia by interfering with the arterial blood supply.

HART, Greenwich, Conn.

CLINICAL ASPECTS OF DISEASES OF THE SPINAL CORD. O. VERAGUTH, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:579 (July) 1934.

Three unusual cases are described. The first case was that of a boy, aged 5 years, who died after a laminectomy; autopsy showed status thymicolymphaticus and an epidermoid tumor under the dura mater between the first and the second thoracic vertebra. The second case was that of a man, aged 37, who was operated on because of symptoms of compression; adhesions were found between the fourth thoracic segment of the spinal cord and the dura. These two cases are discussed from the point of view of being due to some embryologic maldevelopment. The third case was that of a man, aged 40, who showed signs of a compression of the spinal cord in the midthoracic region; a roentgenogram disclosed a platyspondylisis with a high degree of osteoporosis.

MICHAELS, Boston.

Vegetative and Endocrine Systems

THE ANTERIOR PITUITARY HORMONE CONTENT OF THE HYPOTHALAMUS OF DOGS. GIACOMO PIGHINI, Endocrinology **19**:293 (May-June) 1935.

In previous experiments Pighini has shown that the tuber cinereum of man contains a hormonal substance similar to the gonadotropic principle of the anterior lobe of the hypophysis. The present study demonstrates that injections of an emulsion of tuber cinereum tissue from normal dogs into the immature female rat produce maturation of the ovaries and hypertrophy of the uterine tubes, though the changes were less in amount than those obtained by injections of an emulsion of the hypophysis of the ox. The author suggests the possibility of the presence of the follicle-stimulating principle only in the extract of the tuber cinereum tissue, whereas both a follicle-stimulating and a luteinizing factor are present in the extract of the anterior lobe of the pituitary gland. The emulsion of tuber cinereum tissue from dogs previously treated with an extract of the anterior lobe of the pituitary gland did not seem to contain more hormone than that from untreated animals. Pighini states that the presence of an active hormonal substance similar to, if not identical with, the sex-stimulating principle of the anterior lobe of the pituitary gland suggests that its action is in part at least on the cells of the hypothalamus. It probably represents hormone transported from the pituitary gland. It may be, however, that it is secreted in situ, since some authors have ascribed to the cells of this region a secretory function.

PALMER, Philadelphia.

THE POSTERIOR HYPOPHYSIS. E. M. K. GEILING, J. A. M. A. **104**:738 (March 2) 1935.

Geiling, in his discussion of the posterior lobe of the hypophysis, gives the primary structural elements as the neuroglia cells, the pituicytes and the nerve fibers. The neuroglia cells resemble those found elsewhere in the central nervous system. In the pituitary gland some of them have become differentiated to form pituicytes, highly branched cells that have granules in the cytoplasm. The presence and significance of nerve fibers in the posterior lobe are still an open question. None of these structures, with the exception perhaps of the pituicytes, are regarded as secreting elements in the ordinary sense. Geiling concludes that in spite of the huge volume of work on the secretion of the posterior lobe, one cannot assign with certainty any specific physiologic rôle in the animal economy to this potent autopharmacologic agent. Possibly the pressor component acts as an efficient regulator of the exchange of metabolites between the blood and the tissues (capillary hormone) and exercises a renal function, and the oxytocic portion may function during parturition to quicken and render more effective the uterine contractions, which result in the expulsion of the products of conception.

EDITOR'S ABSTRACT.

THE PHYSIOLOGY OF ESTROGENIC PRINCIPLES. EDGAR ALLEN, J. A. M. A. **104**:1498 (April 27) 1935.

Allen stresses the following points in the physiology of estrogenic substances: First, as a major objective, the fundamental endocrine mechanism of the estrous and menstrual cycles has been demonstrated. Active hormones have been isolated, and their relation to one another has been partially worked out. Second, incidental to the first point, the reaction of the rodent's vagina has provided a practicable test for the biologic standardization of therapeutic products, and these have now replaced the inert glandular extracts previously in wide clinical use. Third, the extension of the test to carcinogenic substances and to other substances of similar chemical structure from a wide range of sources is extremely important. In description of some of the carcinogenic and estrogenic substances, the time interval required may be considerably greater than that required for the growth phase of the estrous reaction to theelin. The reasons for variations in the time of reaction are not clear. It is not yet known whether some of the related substances included under the term "estrogenic" will produce more than the vaginal growth reaction. Few of them have been tested as to value in replacing other phenomena of estrus or menstrual phenomena in primates.

EDITOR'S ABSTRACT.

RÔLE OF SODIUM IN ADRENAL INSUFFICIENCY. ROBERT F. LOEB, DANA W. ATCHLEY and JULES STAHL, J. A. M. A. **104**:2149 (June 15) 1935.

Loeb, Atchley and Stahl believe that if adrenal insufficiency in man is not relieved by administration of sodium chloride it will not be relieved by commercial extracts of adrenal cortex given in the usual dosage. It is distinctly hopeful, however, for the future of this type of therapy that the commercial extract is entirely adequate for the healthy survival of the adrenalectomized dog. The studies that the authors' report indicate that there is a definite relationship between sodium metabolism and the active principle of the adrenal cortex. When cortical insufficiency develops, the disturbances in sodium metabolism manifest themselves in a number of ways that have significant diagnostic and therapeutic implications. The concentration of sodium in the blood is decreased because of an increased rate of excretion of sodium. The diagnostic change in the sodium level becomes more apparent and specific when salt is withdrawn from the diet. The withdrawal of salt, however, may result in an adrenal crisis dangerous to the patient. Conversely, the administration of salt will frequently alleviate acute adrenal insufficiency, and the continuation of this therapy mitigates to a considerable extent the signs and symptoms of Addison's disease. When destruction of the adrenal glands is complete, salt alone will not maintain life.

EDITOR'S ABSTRACT.

THE ADRENAL CORTEX. R. F. LOEB, J. A. M. A. **104**:2177 (June 15) 1935.

In his discussion of the adrenal cortex, Loeb states that it has been known for many years that destruction of the adrenal glands in the human being, or complete ablation of these structures in most animal species, results in death. Following the isolation and synthesis of epinephrine, it was shown that this secretion of the medulla of the glands would not maintain life. In human beings suffering from severe Addison's disease, as well as in totally adrenalectomized animals, this hormone, regardless of the dose or means of administration, proved to have little if any therapeutic effect. In experimental animals, extirpation of one adrenal gland and destruction of the medulla in the other led to no apparent deleterious effects; such animals survived indefinitely. Removal or destruction of the cortex of both glands, however, in the absence of sufficient accessory tissue, invariably caused death. Thus it was established that another substance, present in the cortex of the adrenal gland, was essential for life. Further proof of the validity of this idea was provided by the extraction of such a hormone and the demonstration that it would insure the survival of the adrenalectomized animal.

The discussion entails the preparation and assay, the functions and the therapeutic application of the cortical hormone. There is at the present time a tendency toward widespread and indiscriminate administration of cortical extract in small and infrequent doses to all those who are "weary and heavy laden." While this type of therapy may or may not be harmless, it is neither specific nor critically applied.

EDITOR'S ABSTRACT.

PHYSIOLOGY OF PARATHYROID. ADOLPH M. HANSON, J. A. M. A. **105**:113 (July 13) 1935.

Hanson states that the parathyroid glands are concerned with calcium-phosphorus metabolism. Experimental work with animals indicates that calcium-phosphorus metabolism is of great importance in the body because it is necessary to the calcification of bone and teeth. The ionic calcium of the blood serum serves to control the varying normal degrees of irritability of nerve and of voluntary, as well as of involuntary, muscle. Because of this effect on the nerve endings and the involuntary muscle, it also increases vascular tone. It plays an important part in the clotting of blood and milk. That portion of the nonionized calcium which is diffusible may play its part with the ionized form in lessening the irritability of nerve endings and muscle. Little is known concerning these glands so essential to life. The parathyroid glands contain two types of cells: the principal cell and the oxyphil cell. This would indicate that the glands have at least two functions: control of calcium-phosphorus metabolism and another function as yet unknown. Which cell is extracted by boiling in hydrochloric acid and has an active element now recognized as one of the parathyroid hormones is not yet known. Calcium-phosphorus metabolism is concerned not only with the increase of ionic and dialyzable calcium in the blood serum and its normal retention and application to the needs of the entire body but with maintaining the normal calcium-phosphorus balance in the amounts of each within the normal varying degrees of their interrelationships. The parathyroids subserve this function. The fetus is a calcium-phosphorus robber during gestation and lactation, and nature may have provided these accessory glands for the purpose of meeting this as well as accidental demands. The normal amount of calcium in the blood serum in man is generally accepted at from 9 to 11 mg. per hundred cubic centimeters; that of inorganic phosphorus, as an average upper limit of normal, at about 6 mg. per hundred cubic centimeters. In dysfunction of the parathyroid glands due to a deficiency of calcium in the blood serum, varying degrees of hyperexcitability of nerve tissue and muscle may occur. Hyperparathyroidism increases the viscosity of the blood and depletes the calcium of the osseous system. It may rightly be said that the normal function of the parathyroids is to preserve a normal nervous system and normal muscle contractility, including that of the heart, and to bring about and maintain the normal calcification of bone and the calcification of pathologic areas in healing processes. In dysfunction of the parathyroids methylguanidine may occur in sufficient concentration to be toxic. Experimental work and certain clinical observations suggest a detoxifying effect following the injection of active parathyroid extracts. The rôle that the parathyroids may play in maintaining natural immunity and normal healing power awaits scientific proofs to explain certain clinical observations.

EDITOR'S ABSTRACT.

THE THYMUS GLAND. L. G. ROWNTREE, J. A. M. A. **105**:592 (Aug. 24) 1935.

Rowntree avers that uncertainty has characterized the knowledge concerning the thymus gland from ancient down to modern times; its function has remained a riddle. Despite the fact that the gland occurs in all higher animals and in lower orders down to primitive fishes, its nature is not understood. Careful studies on the growth and development of the thymus gland have been made by various workers. Although the literature on the thymus is unusually voluminous, little is known at present concerning its function. Probably the most important and

convincing work yet reported is a series of investigations carried on in Asher's laboratory. Wiktor Nowinski administered an aqueous extract of the thymus gland called thymocrescin to rats and found that, given daily, it overcame the loss of weight of animals incident to a vitamin-free diet. The extract stimulated growth, overcame vitamin deficiency and increased the size of the gonads. Despite all these experiments and thousands of others, doubt has continued to exist relative to the function of the thymus gland in the minds of most physiologists, endocrinologists and clinicians. Clinical studies have also contributed something to the knowledge of the thymus. The gland varies greatly in size in various conditions. There is enlargement in cases of exophthalmic goiter, Addison's disease, acromegaly and status thymicolymphaticus, and supposedly in certain cases of myasthenia gravis and rickets. There is also enlargement after hypophysectomy and adrenalectomy. It is persistent in eunuchs, and its involution is delayed in victims of early castration. The gland is diminished in size after puberty; this fact led Swale Vincent to propose the hypothesis that normal involution of the thymus is due to the development of the reproductive organs. The thymus diminishes in size in instances of starvation, inanition, marasmus and wasting diseases generally. Its enlargement in cases of Addison's disease and exophthalmic goiter constitutes an exception to this rule. The gland is subject to inflammation and infection and to syphilis and tuberculosis and is occasionally the seat of tumor formation. Enlargement or hypertrophy of the thymus is frequently diagnosed. This has been considered of great importance because it is supposed to have led to many tragic deaths in infants and children, an association first noted by Bichat. Status thymicolymphaticus is defined as "a condition in childhood of hyperplasia of lymphatic tissues and of the thymus in association with a flabby fat overgrowth of the body and hypoplasia of the heart and blood vessels. Pathologic examination discloses overgrowth of the body and relatively large heads, hyperplasia of the lymph glands and structures of the tonsillar ring, moderate enlargement of the external and internal lymph glands and hyperplasia of the solitary and agminated follicles of the small and large intestine" and atrophy of the adrenal glands. In the author's work, white rats of the Wistar strain have been given daily for sixteen months intraperitoneal injections of an extract of the thymus gland prepared by Hanson. In the first generation (F_0) treated test animals were heavier, bred more frequently and had larger litters of heavier average weight per rat. Little of note appeared in the second generation in the first six litters, but in the later litters (the seventh to the eleventh) precocity appeared. In the tenth and eleventh litters, the animals were larger than normal, teeth erupted on the second day and the eyes opened on the tenth day. In the animals of the third to the seventh (F_2 to F_6) generation, striking and accruing precocity and acceleration in growth and development, were noted in the offspring of each succeeding generation under treatment. Because of the astounding precocity, a study of the chemistry of the rats' blood was undertaken, which revealed definite changes in the calcium and phosphorus content. Roentgen studies of the skeleton made at weekly intervals revealed marked differences between the skeletons of the controls and those of the seventh generation of rats treated with the extract of the thymus gland. In the test animals (1) there was an increase in all dimensions, particularly in the length of the diaphyses of the long bones, for the actual age of the animals; (2) the centers of ossification of the epiphyses of the long bones were visible earlier; (3) the centers of ossification of the epiphyses of the long bones and the vertebrae calcified and united earlier. Study of the effects of extract on the heart revealed the facts that small doses have little or no effect on the cardiac action and that large doses depress blood pressure and cause death through inducing complete auriculoventricular heart block. The author believes that from the foregoing it is apparent that there is still a state of ignorance rather than of enlightenment relative to the thymus gland. More work is necessary from the standpoint of biology, embryology, histology, physiology, pathology, pediatrics and clinical medicine.

EDITOR'S ABSTRACT.

THE EFFECT OF ANTERIOR PITUITARY EXTRACTS ON ACETONE BODY EXCRETION IN THE RAT. PETER T. BLACK, J. B. COLLIP and D. L. THOMSON, J. Physiol. **82**:385 (Oct. 17) 1934.

Black, Collip and Thomson undertook the study of the effect of an extract of the anterior lobe of the pituitary gland on the excretion of acetone bodies in the rat to see if the acetonuric response to the extract would eventually become diminished or lost and if there were present in the serum of animals treated with thyrotropic hormone a substance which would inhibit the action of thyrotropic extracts. They also sought to prove or disprove the identity of the principle active in this response with the thyrotropic hormone. It was found that a series of rats which had lost their sensitivity to the purified thyrotropic extract showed much less acetone than controls of the same age which had not received the desensitizing treatment. Another group of rats treated with the serum from a horse which had been desensitized to thyrotropic extract did not respond to a thyrotropic extract and excreted no more acetone than the controls.

The authors' work leads them to believe that the ketogenic effect is not a consequence of stimulation of the thyroid gland, as some writers have held, and that it is due not to a thyrotropic substance but to some other active principle in the extracts. This active principle is not identical with the thyrotropic hormone or with the growth hormone. The rapid response to thyrotropic extracts cannot be duplicated with thyroxin. They conclude that the ketogenic principle is only an accidental contaminant in the thyrotropic fractions. The injection of a suitable extract of the anterior lobe of the pituitary gland strikingly increases the amount of acetone in rats, either during a period of fasting of three days or during the administration of a diet of filtered butter. This effect may be obtained with growth-hormone preparations practically free from thyrotropic hormone or with thyrotropic fractions free from growth hormone; it is not obtainable with adrenotropic fractions. The effect may be obtained in thyroidectomized animals and is not obtainable with moderate doses of thyroxin under similar conditions in normal animals. The effect is not obtainable in rats subjected to prolonged preliminary treatment with thyrotropic extracts containing the ketogenic principle. The serum of a horse subjected to prolonged treatment with the thyrotropic extract inhibits the ketogenic action of this extract in young rats during fasting. PALMER, Philadelphia.

THE EFFECT OF OVARIAN HORMONE ON THE PITUITARY, THYROID, AND ADRENAL GLANDS OF SPAYED FEMALE RATS. DOROTHY H. ANDERSEN, J. Physiol. **83**:15 (Dec. 14) 1934.

Andersen reports studies of the effect of estrogenic substance on the pituitary, thyroid and adrenal glands of spayed female rats. It has been demonstrated that as the interval after castration is increased the quantity of estrogenic substance required to produce estrus is increased, and after about six weeks the dose must be high. On the other hand, the weights of the thyroid and adrenal glands do not decrease to a constant level until about six weeks after spaying, and the hypophysis at this time has not yet become as large as it does a few weeks later. In consideration of these facts, Andersen uniformly spayed the animals at from 78 to 82 days of age and began injection after an interval of from forty-one to forty-three days. Estrogenic substance dissolved in ethylene glycol was injected in doses of 5 rat units three times a day for two days, making a total of 30 rat units. Groups of rats were killed at intervals of twenty-four, thirty-six, forty-eight, seventy-two and one hundred and twenty hours after the first injection. The rats were standardized as to strain, diet, care, technic of dissection and weight. The pituitary gland reached its greatest weight in animals killed twenty-four hours after the first injection. These rats had received only 15 rat units of estrogenic substance. The pituitary gland remained at about the same size during the period of observation, namely, until the sixth day of the experiment. The adrenal gland was increased in size in twenty-four hours, but reached its maximum in forty-eight hours and then decreased rapidly in weight. The thyroid gland also

increased in size in twenty-four hours but reached the peak of its weight in seventy-two hours. Andersen's experiments indicate that the normal functioning of the thyroid, adrenal and pituitary glands is dependent on the presence of ovarian hormone. These glands are atrophied six weeks after spaying and can be restored to their normal appearance within a few days by physiologic doses of estrogenic substance. Andersen concludes that injection of ovarian hormone restores the atrophied pituitary, thyroid and adrenal glands of spayed rats to the weight found at estrus in normal animals. The histologic picture of the thyroid and adrenal gland is similar to that of the rat in estrus. These changes in weight are evident within twenty-four hours after the injection of small doses (15 rat units) of the hormone. The maximum response of the hypophysis occurs after twenty-four hours, of the adrenal gland after forty-eight hours and of the thyroid gland after seventy-two hours. A significant degree of hypertrophy of the adrenal gland may be produced by weak estrogenic substance and neutral broth, but not by the injection of nonpotent estrogenic substance. Hypertrophy of the thyroid was produced by the injection of weak and nonpotent estrogenic substance, but not by the injection of neutral broth. The pituitary gland was not affected by the use of either of these preparations.

PALMER, Philadelphia.

PRECOCIOUS PUBERTY DUE TO HYPERFUNCTION OF THE ADRENAL GLANDS AS A STATE OF DEGENERATION. IGNACY PINES, Rev. franç. d'endocrinol. **13**:286 (Aug.) 1935.

Pines reports a clinical case in which there were signs of a disturbance of the endocrine system and stigmas of degeneration in support of Jules Bauer's concept that dysfunction of the endocrine system is an expression of a general state of degeneration which is constitutionally determined. The case is that of a man, aged 23, with pronounced hirsutism, acromegalic features and a large sella turcica. He was seen originally, at the age of 14, by Bauer. At that time there were signs of precocious puberty with retarded growth and premature union of the epiphyses. Bauer considered the condition as precocious puberty due to dysfunction of the adrenal glands. It is of importance that the hirsutism appeared at the age of 9 and that retardation of growth was noted even earlier. At the age of 15 the hair became gray. Progress in school was poor. At the age of 23, when the patient was seen by Pines, the weight was 57 Kg. and the height 145 cm. The neck, the torso and all the extremities were covered with thick black hair, the forehead was high and prominent, the orbits had a mongoloid slant and the face was of the acromegaloid type, with a large nose, which was flat at the base. All the teeth were missing, the tongue was remarkably long and large. The stigmas of degeneration consisted of an open umbilical ring, numerous fibromatous nodules in the skin of the abdomen and a large keloid near the umbilicus. The upper and lower extremities were very short, the hands were large and ungainly and the fingers and toes were large, short and heavy. The phallus was enlarged, but the other external genital organs were of normal size. The blood pressure was within normal limits. Roentgenographic examination of the long bones revealed changes resembling those seen in cases of chondrodystrophy. The sella turcica was very much enlarged. Pines believes that the original genito-adrenal syndrome has, so to speak, changed into one of acromegaly since its original appearance at the age of 9. He explains the retardation of growth by the early closing of the epiphyses and the possible chondrodystrophy. He raises the question whether signs of dysfunction of the adrenal and pituitary glands have developed independently of each other and in this connection discusses Cushing's syndrome, which, though caused by a basophilic adenoma of the pituitary gland, has all the characteristics seen in cases of corticorenal involvement. He mentions the cases described by Falta, Mathias and Jules Bauer in which signs of acromegaly were first seen and later signs of dysfunction of the adrenal glands developed. Pines believes that in his case precocious puberty with hyperfunction of the adrenal glands preceded the syndrome of dysfunction of the pituitary gland. On the whole, he thinks that the patient presents an

agglomeration of abnormal constitutional signs or a "state of degeneration." He emphasizes especially the significance of the stigmas in this combination. He believes that the signs of dysfunction of the endocrine system as well as the stigmas are concomitant phenomena of a degenerative state.

NOTKIN, Poughkeepsie, N. Y.

THE INFLUENCE OF THE VEGETATIVE NERVOUS SYSTEM ON THE THYROID GLAND. O. PEZENIK, Arch. f. d. ges. Physiol. **235**:486, 1935.

The thyroid gland of rats and mice was studied under the fluorescence microscope from one to three hours after stimulation of the sciatic nerve. In the majority of the experiments an increased activity of the gland was observed.

SPIEGEL, Philadelphia.

Treatment, Neurosurgery

JUVENILE PARETIC NEUROSYPHILIS STUDIES: TREATMENT. WILLIAM C. MENNINGER, Am. J. Syph. & Neurol. **19**:257 (April) 1935.

Juvenile dementia paralytica is more resistant to treatment than the adult form of the disease. This is due in part to the facts that the infection is of low grade and that there has been a gross disturbance in the protective function of antibody formation in the child. The fact that young tissue is more easily destroyed is also a possible factor. In 20 per cent of Menninger's own series of forty-three cases, the condition showed some improvement, in 9 per cent it was arrested and in 71 per cent it was unaffected. Including 144 cases reported in the literature, the incidence of marked improvement is 14 per cent and of slight improvement 25 per cent. The prognosis would appear to be better when the interval between onset and treatment is short, when the condition develops in or after adolescence, when the basic mental state is good and, in young children, when a period of normal mental and physical development precedes the onset of symptoms.

In Menninger's series of 43 personally observed cases, 7 patients showed some improvement; all these had fever therapy—1 diathermy, 2 typhoid and 5 malaria. Mercury, arsphenamine and bismuth were ineffective. Three patients received tryparsamide, one of whom showed improvement. Eight instances of the use of diathermy in the treatment of juvenile dementia paralytica are reported in the literature, and 7 of the patients were reported as improved. Intensive, prolonged treatment with fever, tryparsamide and the heavy metals is recommended as the best therapy.

DAVIDSON, Newark, N. J.

SYMPATHECTOMY FOR RETINITIS PIGMENTOSA. ALEXANDER E. MACDONALD and KENNETH G. MCKENZIE, Arch. Ophth. **13**:362 (March) 1935.

In September 1930, Royle stimulated interest in the treatment of retinitis pigmentosa by stating that the vision of patients with this disease could be improved by the surgical interruption of the sympathetic nerves to the eye. MacDonald and McKenzie present their experiences in four cases in which this form of treatment was used. From the beginning they were critical of the results, but they believed that the proceduce was warranted in dealing with a condition generally regarded as hopeless. The four cases are presented in detail, with studies of the visual fields and genealogical tables and in one instance with photographs of the fundus. The patient in case 1, who was the oldest of the four and who had had impaired vision for fifteen years, derived no benefit from the operation. The patient in case 2, aged 24, had had an obvious defect at the age of 7. Both fields were small after the operation, the right decreasing possibly less than the left; the results in this case must also be classed as a failure. In the patient in case 3, aged 25, the changes in the fundus and the large ring scotoma seemed to indicate ocular trouble of a longer duration than the history suggested. There

was a definite increase in the field on the side on which the operation was performed. The patient in case 4, aged 25, who had presented a history of grave ocular disturbance, seemed to the authors to be unduly encouraged with the small temporal field that could be demonstrated as a result of the operation.

MacDonald and McKenzie conclude that if operation could be performed early in cases of retinitis pigmentosa, it is likely that more definite conclusions could be reached concerning its value as a means of treatment.

SPAETH, Philadelphia.

BILATERAL RETINAL GLIOMA TREATED BY RADIATION. A. G. FEWELL and W. E. FRY, Arch. Ophth. **14**:190 (Aug.) 1935.

Treatment for bilateral retinal glioma has undergone some changes within the past few years. As recently as 1929, Foster Moore stated that in a case of bilateral retinal glioma in which the tumor in the second eye was only slightly larger than the optic disk, "on advice of colleagues at Moorfields, both eyes were enucleated." His comment on the procedure later was that "in the light of our present experience, we should not again entertain the immediate removal of such eyes, nor consider it the proper procedure." Fewell and Fry are wholly in accord with this. They state that in cases of bilateral retinal glioma in which one eye retains useful vision and in which ophthalmoscopic examination indicates that in all probability the optic nerve head is not involved, the proper procedure after enucleation of the first eye is irradiation of the second eye. They present a case illustrating this in detail. The second eye of their patient contained three tumor masses and was irradiated for a year. At first there was shrinkage, followed later by a proliferation of the tumor, so that enucleation of the second eye became necessary.

SPAETH, Philadelphia.

IRRADIATION IN THE TREATMENT OF TUMORS OF THE PITUITARY GLAND: REPORT OF TWENTY-THREE CASES. CARL W. RAND and RAYMOND G. TAYLOR, Arch. Surg. **30**:103 (Jan.) 1935.

On reviewing the literature on the irradiation of tumors of the pituitary gland, Rand and Taylor conclude from the European literature that "the consensus seems to be that temporary improvement of visual disorders resulting from the pressure of a tumor of the pituitary gland on the optic chiasm follows high voltage treatment" and, again, that "acromegalic symptoms in general have been arrested by high voltage treatment." In a review of the American literature they found that Frazier warned against procrastination, especially when vision is failing, and pointed out that irradiation will not affect a cystic lesion of the pituitary gland and that there is no way of determining the exact nature of the lesion except by operation. Towne, on the other hand, reported favorable results of long standing with roentgen therapy and expressed the belief that with failure a diagnosis of cystic tumor favorable for operation might be made. Towne was of the opinion that all adenomas of the pituitary gland should be treated with roentgen therapy under the observation of the ophthalmologist and the neurosurgeon and that surgical measures should be resorted to in less than six months only when the visual acuity and fields diminish in spite of roentgen treatment.

Elsberg, according to Dyke and Gross, thought that every patient showing defects of the visual fields as a result of a neoplasm of the pituitary gland should first be given high voltage irradiation. This should be continued if followed by improvement. If the visual fields and acuity diminish, surgical intervention is indicated. Irradiation can be used as a diagnostic test to determine when immediate operation is required and when it is not.

According to Heuer, roentgen therapy is effectual in both the chromophil and the chromophobe type of tumor. Sachs favored surgical intervention but admitted that high voltage therapy was effective for the chromophil type and should be tried before operation. Cushing expressed the belief that the chromophil types

are "more definitely susceptible to radiation," but was not in favor of this type of treatment. Homans admitted the effectiveness of the roentgen rays as did also Bailey, in selected controlled cases. Globus was of the opinion that surgical measures have given the best results.

Rand and Taylor have attempted to estimate the value of high voltage irradiation in the treatment for various types of tumor of the pituitary gland. They have studied twenty-three cases, which include five of the chromophil type and thirteen of the chromophobe type, three of cystic chromophobe adenoma and two of adenocarcinoma. They find that the chromophil type reacts most favorably to high voltage roentgen therapy. In their cases visual improvement has been maintained for from four months to nine years. They do not report any cases of basophil adenoma but mention that reports seem to indicate that this type also reacts favorably to irradiation. They point out that some believe that the eosinophilic and basophilic cells are of a higher type than the chromophobe cells. They should, theoretically, be more resistant to irradiation but, on the contrary, they react most favorably.

The reactions of chromophobe adenomas to irradiation have been variable; the authors find this difficult to explain but suggest that it may be due in part to insufficient dosage and number of treatments. They recall also that tumors of the pituitary gland are not necessarily of a consistent structure but may in some degree contain a mixture of cell types. In some cases slight improvement of vision was noted for a short time, while in others an unlooked for improvement occurred and was maintained. In cases in which there was no improvement and vision continued to fail, the tumor was found to be cystic as a rule. Cystic chromophobe adenomas show no improvement under roentgen treatment. Rand and Taylor think that this fact, in conjunction with the clinical findings, may be used as a point in differential diagnosis from the noncystic tumors. Adenocarcinomas of the pituitary gland do not react favorably to high voltage roentgen therapy.

Certain patients with tumors of the pituitary gland gain from moderate to useful vision after irradiation. In some this improvement may be maintained for years, whereas without it the patient would almost certainly have become blind. Rand and Taylor noted no definite regression in general acromegalic symptoms after irradiation, but neither did they observe any advance during the periods of observation.

Rand and Taylor note the satisfactory results from partial surgical removal of tumors of the pituitary gland but note also that late results are seldom given. In their experience patients who have been subjected to operative treatment alone have maintained improved vision for an average of from one to three years. Surgical intervention followed by high voltage irradiation is a more or less routine therapeutic measure in various clinics. The authors suggest that in selected cases roentgen therapy might be used first in the hope that it might suffice without recourse to operation. They add that these cases should be closely followed, especially with regard to the eyegrounds and visual fields, by the neurologic surgeon. "For at best, high voltage irradiation will give satisfactory results in only a certain percentage of cases. It does not replace surgical procedure, but rather acts as an adjunct to it."

ELVIDGE, Montreal, Canada.

MULTIPLE MENINGIOMAS: REPORT OF A CASE IN WHICH THREE INTRACRANIAL MENINGIOMAS WERE REMOVED SUCCESSFULLY. JOHN E. RAAF and W. M. CRAIG, Arch. Surg. **31**:601 (Oct.) 1935.

Removal of multiple meningiomas by operation with relief of symptoms is of such rare occurrence that it warrants comment. A review of the literature fails to reveal a similar case, although multiple meningiomas have been reported at necropsy. They are frequently associated with acoustic neuromas or generalized neurofibromatosis. The case reported illustrates the difficulty in some instances of localizing and determining the pathologic nature of an intracranial lesion prior to surgical exposure. One tumor was found in the posterior part of the inferior

left frontal convolution and was removed with its dural attachments. When the dura was incised forward, a second tumor was found and removed. Since the presence of these tumors did not explain the high degree of papilledema, or the weakness of the right arm, further search was made, and another tumor was found, compressing the left motor cortex near the arm area. These tumors were all meningiomas but varied greatly in gross as well as in microscopic appearances.

GRANT, Philadelphia.

MYASTHENIA GRAVIS: EFFECT OF TREATMENT WITH ANTERIOR PITUITARY EXTRACT. HAROLD E. SIMON, J. A. M. A. **104**:2065 (June 8) 1935.

Simon states that the number of cases available for the study of the effect of subcutaneous injections of an extract of the anterior lobe of the pituitary gland in the treatment of myasthenia gravis is too small and the period of time over which they have been observed is too short to permit general conclusions, but the results so far are very encouraging. Both of his patients presented undoubted clinical evidence of myasthenia gravis. In both instances the response to the injections of the extract was prompt and complete, and a relapse promptly followed when the treatment was omitted. On the resumption of the therapy the symptoms again promptly disappeared in both cases. Since no other treatment was employed, it would seem justifiable to conclude that this preparation had a marked beneficial effect on all the clinical manifestations of myasthenia gravis in these two cases. In the first case it was possible to discontinue the treatment after four and one half months without recurrence of symptoms. It is impossible to determine whether this was the result of the fortuitous occurrence of a remission or whether a remission was induced by the treatment. In the second case it has been necessary to continue the treatment and during cold weather to increase the frequency of the injections in order to keep the patient clinically well. Whether a remission will be induced or not remains to be seen. In no instance have any untoward effects, either local or general, been observed as a result of the injections. The oral administration of the extract would be preferable to its use hypodermically, if it should prove as efficient. It is planned to try the relative merits of the two methods of administration.

EDITOR'S ABSTRACT.

EXPERIENCE WITH ERGOTAMINE TARTRATE IN ONE HUNDRED AND TWENTY PATIENTS WITH MIGRAINE. WILLIAM G. LENNOX and THEODORE J. C. VON STORCH, J. A. M. A. **105**:169 (July 20) 1935.

Lennox and von Storch treated 120 patients suffering from severe periodic headaches with, in addition, one or more of the following satellite symptoms: hemicrania, nausea or vomiting, visual disturbances, vasomotor disturbance and malaise. They failed to obtain relief from other drugs or treatment, and each gave a history of migraine in other members of the family. Twenty-three of the patients were males, and 97, females. Of the 109 patients who received ergotamine tartrate by intravenous, intramuscular or subcutaneous injection, the result of the first administration was abrupt and complete relief in 90 per cent, slight or temporary relief in 4 per cent and no benefit in 4 per cent; the headaches were made worse in 2 per cent. Of the 11 patients who received medication only by mouth, the first trial was followed by relief in 82 per cent, while in 18 per cent the headaches became worse. Of the whole group of 120 patients, 107 experienced abrupt and complete cessation of the headache with the initial use of ergotamine. Nineteen patients have used ergotamine for more than a year, and all but 1 have obtained relief on each of the repeated occasions on which the drug has been used. In some patients a tendency for the headaches to recur at more frequent intervals or the appearance of unpleasant accompanying symptoms limits the use of the drug. Ingestion is relatively ineffective. The mechanism by which relief is obtained is as yet unknown.

EDITOR'S ABSTRACT.

JUVENILE DEMENTIA PARALYTICA, WITH ESPECIAL REFERENCE TO ITS TREATMENT WITH MALARIA. UDO J. WILE and EUGENE A. HAND, J. A. M. A. **105**:566 (Aug. 24) 1935.

During a period of seven years Wile and Hand observed thirty-one cases of juvenile dementia paralytica, which they discuss with especial reference to a comparison of the status of patients who were given malaria treatment with that of patients who were not. Answers were received to twenty-four of the thirty-one queries sent out. Seven of the patients were dead, and in seven the condition was unchanged; eight of the patients were worse, and two were improved. The results were more unfavorable in patients showing marked involvement at the time of diagnosis. Slightly better results were found in patients over 20 years of age. Most of the fifteen patients who did not receive malaria therapy were treated with preparations of the heavy metals. Most of those who received malaria also had the benefit of this type of therapy. Of those who received malaria, an answer was received from fourteen; two were dead; the condition in four was unchanged; in six it was worse, and in two it was improved. Of the fifteen who did not receive malaria, an answer was received from ten; the condition was unchanged in three and worse in two, and five were dead. The group who received malaria were in somewhat better mental condition at the time of diagnosis, which may account for some of the statistical improvement. Only one patient is now able to cope with his environment at this time, a man aged 26 at the time of diagnosis in 1927. All the others about whom a report was received are dead, are living a vegetative existence in an institution or at home or are so mentally or physically retarded as to be almost a total loss to their families. The cases suitable for malaria treatment are those, it would seem, in which the diagnosis is made by a routine examination of the spinal fluid before any clinical symptoms or signs have appeared, or those in which the mental changes are very mild and have come on fairly late in adolescence or in early adult life. Such cases of the juvenile type are rare.

EDITOR'S ABSTRACT.

TREATMENT OF NINETY-SIX PATIENTS WITH NEUROSYPHILIS BY ACTIVE IMMUNIZATION WITH NONPATHOGENIC CULTURES OF SPIROCHAETA PALLIDA. L. BENEDEK, Monatschr. f. Psychiat. u. Neurol. **88**:1 (Feb.) 1934.

Benedek treated ninety-six patients suffering from neurosyphilis with injections of Hilgermann's cultures of living but avirulent spirochetes. There were fifty-six patients with dementia paralytica and thirty-three with tabes. The group included elderly persons who were in poor physical condition. There was no evidence to suggest that the transfer of the avirulent strain of spirochetes to the human organism could activate the spirochetes and lead to a generalized or localized superinfection. However, focal nervous symptoms were sometimes increased temporarily. Thus, all but six of the patients with tabes showed an increase of such symptoms as lightning pains, gastric crises and paresthesia during the course of treatment. As a rule, a slight to moderate rise of temperature and moderate leukocytosis occurred. Local cutaneous or connective tissue reactions were noted in eleven patients after repeated injections of the vaccine. The formation of abscesses was observed in three patients. This was probably due to contamination of the cultures with other bacteria. Seventy-five patients had previously received some form of treatment, but only eight had shown improvement. This number includes two who had complete remissions. In sixty-nine cases the cultures of spirochetes were given in conjunction with other types of therapy. The latter consisted of one course of treatment with antisyphilitic drugs in thirty-one of these cases. Fifty-five patients showed improvement during or shortly after the administration of the vaccine; the condition of twenty-four patients was unchanged, and ten became worse. One patient died during treatment, but necropsy disclosed a neurinoma of the cerebellopontile angle as the cause of death. It was possible

to follow seventy-five patients for approximately from two to three years. Complete remission had occurred in thirteen, considerable improvement in twelve and slight or moderate improvement in fifteen. Sixteen members of the group had died. Better results were noted in the group with tabes than in that with dementia paralytica, 54.5 per cent of the patients in the former and 25 per cent of those in the latter group showing improvement.

The serologic reactions were studied in fifty-one cases. The Wassermann reaction of the blood became negative in four cases and that of the spinal fluid in seven cases. The colloidal gold reaction showed improvement in 49 per cent of the group, and the cell counts were diminished in 52.9 per cent. It was not possible to determine whether there was any correlation between clinical and serologic changes owing to the fact that the lumbar punctures were performed without regard to the clinical condition of the patients. A scrutiny of the results obtained in patients treated solely with injection of spirochetes leads Benedek to conclude that vaccine therapy is as efficacious as other forms of treatment. The results are favorable enough to suggest that with further development of the method still greater success in treatment may be obtained.

ROTHSCHILD, Foxborough, Mass.

Muscular System

AMINO-ACID—GLYCINE—THERAPY IN THE MYOPATHIES. Editorial, J. A. M. A. **103**:2031 (Dec. 29) 1934.

Recent investigations of the influence of amino-acid therapy on the unbalanced creatine-creatinine metabolism associated with certain types of myopathies have yielded interesting results. These appear to be of particular significance when the alterations in creatinuria are related to the favorable prognosis in this clinical syndrome. Gibson and Martin (*J. Biol. Chem.* **49**:319, 1921) and Brand, Harris, Sandberg and Ringer (*Tr. Internat. Physiol. Cong.*, 1929, p. 29) were among the first to recognize the importance of amino-acetic acid in their investigations of the origin of creatine. The latter workers showed that the ingestion of this amino-acid or of gelatin, which is high in it, by patients with progressive muscular dystrophy was followed by a large increase in the creatinuria. This significant relationship between amino-acetic acid, a substance that the normal person can readily synthesize, and creatine, which has been demonstrated to play an important part in muscle function, suggested to several investigators that the prolonged administration of the amino-acid might have an influence on the clinical and metabolic course of muscular dystrophy. Striking confirmation of this hypothesis was reported from the laboratory of Karl Thomas in Leipzig (*Proc. Soc. Exper. Biol. & Med.* **28**:609, 1932; *Deutsche med. Wchnschr.* **59**:169, 1933). Six cases were studied during eight experimental periods each of a few months' duration. The daily ingestion of from 15 to 20 Gm. of amino-acetic acid increased the daily excretion of creatine to a value that was from 100 to 1,000 per cent higher than the previous value observed. After a period of weeks the excretion of creatine began to decrease despite the continued administration of amino-acetic acid, falling finally to the former control level. Coincident with this diminished creatinuria there was an increased excretion of creatinine and an improvement in the patient's ability to retain ingested creatine. These interesting alterations in the metabolism were accompanied by remarkable improvement in the condition of the patients. Muscles that previously had felt tired now seemed refreshed, and the patients often expressed the desire to make muscular movements that had not been possible for a considerable period. Interruption of the treatment with amino-acetic acid resulted in a gradual disappearance of the improvement, and the disease eventually returned to its previous status. Resumption of the administration of amino-acetic acid again resulted in the previously described improvement.

These important results have stimulated many clinicians to use amino-acetic acid, with and without ephedrine, in the treatment of various types of myopathy. However, conflicting opinions have arisen regarding the various metabolic relationships and therapeutic effects following either amino-acetic acid or glutamic acid therapy, the latter amino-acid having also been found to be efficacious by some workers. This disagreement is probably due to a considerable extent to the failure to distinguish accurately the various types and stages of muscular dystrophy and to evaluate correctly those muscular atrophies which are secondary to pathologic lesions in the central nervous system. A good summary of this literature, together with an account of metabolic studies on thirty-four patients, representing eleven distinct types of myopathy and atrophy, has been recently presented by investigators of the Louisiana State University Medical Center (*J. A. M. A.* **103**:1595 [Nov. 24] 1934). Either amino-acetic acid or glutamic acid therapy was demonstrated to be capable of augmenting the creatinuria present in each of ten different types of cases. Concomitant with this increased excretion of creatine, an objective and subjective improvement was present, the magnitude of which was dependent on the nature of the myopathy. In general, the conditions classified as primary myopathy and myasthenia gravis showed distinct clinical improvement, except in a few cases of the former type in which the disease had advanced to the stage of complete muscle degeneration. However, while some of the muscular dystrophies were greatly benefited, no objective improvement was observed in the neuromuscular atrophies, despite the fact that the creatinuria present was influenced by the amino-acid therapy. In a few instances of the latter disease there was subjective improvement or merely an arrest of symptoms.

These investigations serve to emphasize anew the importance of the amino-acid therapy for certain of the myopathies, to add metabolic evidence of the differences existing among these various muscle diseases and to elucidate the function and importance of creatine and precursors of creatine in muscle physiology.

EDITOR'S ABSTRACT.

PROGRESSIVE MYASTHENIA WITH PARTICIPATION OF THE SMOOTH MUSCLES OF THE EYE. V. RABINOVITCH and G. VENGRJENOVSKY, Rev. d'oto-neuro-opht. **12**:758 (Dec.) 1934.

Progressive myasthenia has been considered a primitive disease of striated muscles, although isolated cases have been observed in which the manifestations have extended to the smooth muscles of the urinary bladder and to the intrinsic muscles of the eye. In the case reported, the patient, a laborer aged 22, complained of visual disturbances, diplopia and ptosis of the right eye. The trouble began at the age of 12, following a violent fright, and progressed slowly. Examination revealed pupils that were equal but continually varied in size, with narrow palpebral slits and ptosis. While the patient was fixing on an object, diplopia appeared after ninety seconds and was relieved by closing the eyes. Consecutive tests showed a progressively shorter interval of freedom from diplopia after fixation. When the patient followed the finger with the eyes for ninety seconds, convergent strabismus appeared but was quickly relieved by rest. Convergence was intact at first, but marked insufficiency of the internal rectus muscles soon occurred. A similar fatigability was observed when the patient attempted to accommodate: the near point receded rapidly until after four minutes reading was impossible. Visual activity varied from 0.3 to 0.8, and glasses did not improve it. Skiascopic examination revealed bilateral myopia, varying from 1 to 3 and 4 diopters; after atropinization the myopia was replaced by hyperopia of 1.5 diopters. The orbicularis, the frontalis, and the extensor muscles of the neck exhibited marked fatigability. No additional abnormalities were discovered.

Besides essential myasthenia, symptomatic myasthenia may follow typhus, epidemic encephalitis, malaria, diphtheria and tuberculosis. No cases of fatigability of the ciliary muscle in myasthenia were discovered in the literature. Fatigability of the ciliary muscle in a myasthenic patient must be considered a myasthenic phenomenon. This view harmonizes with the modern conception of myasthenia:

that it is an essential disturbance of the function of the sarcoplasm of striated muscles. This function is identical with the function of smooth muscles; both are characterized by tonic contraction. Participation of the smooth muscles in myasthenia is explained by the neurovegetative theory of this condition. There is certainly a hypofunction of certain sympathetic fibers going to the myasthenic muscles, which is proved by: (1) aggravation of the myasthenic symptoms by the action of ergotamine, which paralyzes sympathetic filaments; (2) extreme fatigability in Addison's disease, and (3) extreme fatigability in muscles from which the sympathetic supply has been removed. If it is true that myasthenia is caused by disease (infection) of the meso-encephalic and diencephalic neurovegetative centers, with consecutive hypotonia of the sympathetic nerve, the spasm of accommodation may be the effect of secondary vagotonia. Instability of the tonus of the ciliary muscles may explain the variations in refraction observed in the case reported.

DENNIS, San Diego, Calif.

THE DOUBLE REACTION OF MUSCLES IN MYOTONIA (ELECTRICAL STUDIES). F. KRAMER and F. QUADFASEL, Monatschr. f. Psychiat. u. Neurol. **87**:252 (Dec.) 1933.

In the myotonic reaction electrical excitation of nerve and muscle produces different results. When the nerve is stimulated with the faradic current the only pathologic phenomenon is the persistence of the contraction after cessation of the stimulation. The reaction elicited by applying a constant current to the nerve does not deviate from the normal. On the other hand, direct excitation of the muscle with the galvanic current causes a sluggish and irregular contraction resembling that occurring in the reaction of degeneration. This reaction is obtained in a clear form only when the muscle is stimulated at a considerable distance from the motor point. If the electrode is placed on the motor point, the contraction is similar to that occurring on indirect stimulation through the nerve trunk. Kramer and Quadfasel studied this double reaction of the muscles in two cases of myotonia congenita, in one case of myotonia atrophica and in one case presenting a mixed picture suggestive of a transitional state between Thomsen's disease and myotonia atrophica. In all cases it was found that when motor points were used the chronaxia values were within normal limits, whereas very high values were obtained on more distal stimulation, which caused sluggish contractions. Investigations by means of interrupted continuous currents also showed that direct excitation of the muscle and indirect stimulation produced different results. With indirect stimulation normal reactions were observed. According to the authors, the abnormal reactions obtained on direct excitation owe their origin to the fact that under direct excitation accommodation occurs more slowly and persists for a longer time than when indirect stimuli are applied.

ROTHSCHILD, Foxborough, Mass.

A FAMILIAL CASE OF MYOTONIA ATROPHICA. N. KRYSCHOWA and H. BAJEVSKAJA, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:507 (July) 1934.

The patient, a man aged 46, who originally came from a region near Moscow, U. S. S. R., had shown progressive atrophy and weakness of the muscles of the neck, face and upper and lower extremities since the age of 20. Myotonic manifestations accompanied the atrophy. In addition to ataxia and reflex changes, which were not very marked, a series of changes in the endocrine-vegetative status and a peculiar mental state were present. The familial history revealed that the patient's father had had a similar illness, a cousin had presented a rudimentary form of the disease and many relatives had had cataracts. It is concluded that the hereditary form of myotonia atrophica is an irregularly dominant one and that the cataract is apparently the expression of a pleiotropia of the genes. Rudimentary forms may occur in the same family.

MICHAELS, Boston.

Special Senses

HUMAN RODS AND CONES. G. L. WALLS, Arch. Ophth. **12**:914 (Dec.) 1934.

This paper is an ophthalmologic review of the literature on the subject of human rods and cones, its object being to present the state of knowledge as it exists at this time. Advance in the knowledge of the histologic structure of the human retina practically ceased with the publication of Greeff's classic monograph in 1900, but photochemical and photophysical theorization as to the nature of the visual process continues. Walls first discusses the size and form of the rods and cones. He believes that there is good reason to doubt the normality of some of Greeff's drawings. He states that the true size and form of extrafoveal cones must be considered as unknown and that it is idle to quote dimensions as given by various authors. Reliable and closely agreeing figures for the rods and for the inner segments of the cones are correct as they appear in any standard work on ophthalmology. He does not agree with Parsons that elongation in the shape of the cones at the fovea is an indication of the assumption of the function of the rods by the foveal cones.

A discussion of the numbers of the rods and cones in the human eye, both for an absolute and for a relative consideration, in Walls' opinion is not a matter of purely academic interest. He thinks that reliable figures for these are still not available. They will be obtained eventually, but not until the problem of fixation of retinal tissue without distortion has been solved. Of the estimates made, those of Krause—800,000 optic nerve fibers, 7,000,000 cones and 130,000,000 rods—were the most painstakingly computed. Ramón y Cajal's work revealed that most of the summation is in the rod bipolars, the peripheral cones being divided by synapses into other rod bipolars and the foveal cones each having a neuron to itself. Probably a majority of the afferent optic nerve fibers carry impulses from the cones, but the relative number of optic nerve fibers of the rods and cones can only be guessed. The brute character of scotopic vision, apart from the effect of dilatation of the pupil, is due entirely to the large area of the visual field subtended by a single scotopic cortical element, in contrast to the more nearly point-for-point correspondence of the objective and subjective visual fields when the pure-cone, "fine-grained" fovea is in operation in intensities above the threshold for the cone.

In regard to the number of cones in the fovea and the number per unit area in that all-important region, there are contradictory reports, because of differences in fixation. The anatomic preservatives which prevent foveal rupture make it impossible, unfortunately, to distinguish a macular cone from a rod, and the shrinkage of the retina in all histologic preservatives stretches and ruptures this region, which is thin and therefore weak. The resultant distortion renders precise mensuration as well as definite determination of the form impossible. There is no general agreement as to the diameter of the rod-free area, and estimates—between which no choice is possible at present—ranging from 4,000 (Krause) to 13,000 cones (Becker) in this area are mentioned by Greeff.

The relationship of the rods and the cones to contiguous structures is next discussed. Walls speaks of the mode of attachment of the visual cells to the external limiting membrane as of an unknown nature. Greeff's description of the inner segment of the rod showed it tapering to a point at the membrana limitans. Walls believes that this is wholly false, for while the fibers of the rod do become filamentous they are found some distance below the membrana limitans. He speaks highly of Garten's superbly fixed sections of cones from the Macacus rhesus. He discusses also the appearance of a cone which he believes has not been reported before. It was seen in preparations made by Judd of Detroit and later was confirmed in sections made by Walls. The entire complexity of the cone fits neatly into the popular notion that the cone is more highly metabolic than the rod.

As for the cytology of the rods and cones, the only points which are beyond argument are that the outer segment is doubly refractive, its ground substance is lipoid, it has a thin sheath, which in the case of the rod is open at the tip, and it contains a material called "myeloidin." The question which is in most urgent need of answer is whether a portion of the contents of the outer segment is organized into a pile of disks. These are placed, if present, transversely in the outer segment, with a small amount of another material, of different refractive index, around and between them. This appearance is often afforded by slender outer segments stained with hematoxylin; but an alternative explanation, first offered by W. Krause, that the "disks" are only turns of a tightly wound spiral filament or filaments, has as much or more evidence behind it.

It is the possible optical behavior of these hypothetic disks, provided they exist —their action as a mirror, as an échelon or as a tuned and resonant system— which accounts for the great interest in this otherwise minor and academic point. The possible significance of the presumptive spiral threads is of scarcely less interest, though to a different group of investigators—those concerned with the problem of the nature and ancestry or former condition of the visual cells of vertebrates—for though the spiral filaments have often been considered as neurofibrils they are open to another interpretation in connection with a theory that the visual cells are not neurons or neuro-epithelium but rather sensory ependymal cells. Physiologic speculation is idle as long as the question of cytology remains open. It seems, however, that if the difficulty lies in the fact that both spiral and discoid organizations can and do occur in different animals, then neither arrangement can be essential for vision.

Another filament system, of dubious physiologic importance but of great interest from the standpoint of the history of the visual cells, is the centrosomic system. It is undeniable that all types are found throughout the retinas of submammalian and mammalian species.

The marked differentiation of the nuclei of human rods and cones has long been known. So, also, is there a difference in the distribution of chromatin. Another striking difference occurs in the foot-pieces. Still further dissimilarities occur in the retinas of other mammals and of amphibians.

The locus of reception is next considered. Since linear chromatic aberration of the human eye is greater than the thickness of the retina, it is erroneous to speak of a retinal level at which the image lies. The problem involved is the same whatever way it is expressed: At what level of the retina does reception take place? Which part of the visual cell is the recipient one, capable of converting photic energy into a nerve impulse? All types of experiments have been made to determine this. It is rather to be expected that the outer segment of the visual cell should be the locus of reception. To allocate reception further, to the peripheral centrosomic fiber or to the myeloidal spirals, as some are inclined to do, is impossible at present.

The seemingly impregnable duplicity theory expresses the physiologic contrast between the rod and the cone. The rod is concerned with achromatic vision and when adapted to dark is very sensitive, but it yields only hazy central images because of the summation in bipolar and ganglion cells which materially helps to confer the sensitivity. The cones afford chromatic and achromatic sensations and function only in brighter light. They yield detailed subjective pictures, since there is less summation throughout the retina and none in the fovea.

The assumption that the function of the rods in relation to vision is a simpler process than that of the cones is scarcely justified, but so long as this is understood there will be no harm in considering first the behavior of rods. These cells are remarkable for their capacity for dark-adaptation, a phenomenon so complex in all its aspects as to have given rise to an extensive literature, which has recently been most ably reviewed by Adams. This capacity is greatly impaired by a deficiency of vitamin A, which is believed either to retard the formation of rhodopsin (visual purple) or to diminish the maximum amount producible, probably the latter.

It is the formation, not the "regeneration," of rhodopsin in dim light which constitutes by far the most important factor in promoting the great sensitivity of the scotopic rod. Interest in rhodopsin, dormant since the heyday of the Heidelberg school, led by Kühne, is now being revived.

Hecht has hypothesized the nature of the photochemical process involved in vision, and not much has been added to this since, though other authors have criticized his theories without making substitutions. It is a fact that the curve produced by the bleaching of rhodopsin in monochromatic lights and the absorption spectrum of its solutions agree closely with the curve of luminosity of the scotopic spectrum. Even if rhodopsin is merely a sensitizer, it still is much the determinant of the behavior of the entire scotopic retina. The author thinks that the evidence available points to the cone as the more primitive visual cell and that the steps in the manufacture of rods from cones can actually be seen in extant kinds of animals.

There is no doubt that a survey of the myriad of hypotheses which have been formulated relative to color vision shows gross inconsistencies. There is only one physical theory concerning color perception which the author thinks is worth considering, and even this he dismisses in view of the fact that it is based on the disks of material in the outer segment, which he has noted as probably nonexistent. Each disk is tuned or resonant to a particular frequency, the red end of the spectrum being perceived by the disks at the tip of the outer segment and the violet end by the disks at the base, and the myoid cone has a range of contraction and elongation of 225 microns in light and in darkness.

Apart from the precarious reasoning concerning the "disk," this theory is invalidated by the assumption of migration of the cones alone, for no such phenomenon has been detected in the human retina, and even if it occurs it would have been noticed long since if the distance of migration even approached the thickness of the entire retina—a distance several times that covered by the exceedingly mobile cones of the frog.

SPAETH, Philadelphia.

ACUTE OPTIC NEURITIS IN DEMYELINATING DISEASES OF THE NERVOUS SYSTEM. MILTON L. BERLINER, Arch. Ophth. **13**:83 (Jan.) 1935.

So-called demyelinating diseases of the nervous system are reviewed. In this category are included disseminated (multiple) sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica (Devic's disease) and encephalitis periaxialis diffusa (Schilder's disease). The neurologic literature discloses much that is contradictory as well as overlapping. It is not impossible that all these conditions are variations of one main entity and that their clinical differences are due merely to degrees of involvement or to predilection for special tissues. The current belief as to their etiology is that they are of infectious origin and that they are probably due to some neurotropic virus which is disseminated by the blood stream or by the cerebrospinal fluid. The observations common to all are perivascular infiltration, demyelinization, degeneration of the axis-cylinders and glial activity.

Involvement of the optic nerves, chiasm and tracts may occur in all these diseases. Sometimes there seems to be a distinct affinity for these structures, which is not surprising when one considers that they are really brain tracts. Owing to the anatomy of the optic nerve, it is natural to find the morbid processes in its retrobulbar portion, where the nerve fibers are myelinated. Consequently, only when the disease is extensive or when it occurs far forward, near the lamina cribrosa, is an extension of the acute reaction visible in the intra-ocular portion of the optic nerve. No one has reported as yet the presence of the disease in the retina, which might happen in the presence of a patch of medullated nerve fibers. When one speaks clinically of acute optic neuritis in regard to the demyelinating diseases, one means acute retrobulbar neuritis that has manifested itself by edema and congestion in the papilla. The ophthalmoscopic picture varies from slight blurring of the margins of the disk to definite swelling of the entire surface. The

swelling seldom measures more than 1 or 2 diopters of elevation. Because of the immediate and usually profound loss of vision, the edema of the optic disk in these diseases will not be confounded with that of early papilledema due to increased intracranial pressure in which the visual disturbance comes on later and is gradual.

In demyelinating diseases of the central nervous system an acute reaction may occur in the optic papilla (acute optic neuritis). Although in the present stage of knowledge of the demyelinating diseases there seems to be little histologic difference among them, clinically certain well defined types appear. In acute disseminated sclerosis there seems to be a unilateral appearance of acute optic neuritis, with a decided tendency to remissions. In neuromyelitis optica, bilateral involvement of the optic nerves, associated with myelitis and with a decided tendency to recovery, is the rule. Acute encephalomyelitis likewise may be characterized by bilateral involvement of the optic nerve, associated with a special disposition to involvement of the optic tracts and with little or no tendency to recurrences. It appears that in Schilder's disease, which is generally fatal in youth, acute optic neuritis is not so frequent as in other types of demyelinating diseases. Here the process principally affects the higher centers. In acute encephalomyelitis and neuromyelitis optica the tendency is toward extensive involvement of the optic nerve, and consequently acute optic neuritis appears frequently. In disseminated sclerosis, in which the lesions are more circumscribed, the classic type of axial retrobulbar neuritis occurs, that is, neuritis without reaction in the nerve head, save in the types in which a patch is situated just behind the lamina cribrosa, when a visible reaction (optic neuritis) may be observed ophthalmoscopically. This reaction may be slight and is often not diagnosed. It seems that acute optic neuritis occurs more frequently in disseminated sclerosis than a study of the literature indicates. Appearing as the primary episode in the disease, it has repeatedly been ascribed to other conditions, chiefly to infections of the posterior nasal sinuses.

Finally, special attention is called to the susceptibility to involvement of the visual pathways in all so-called demyelinating diseases of the nervous system and to the fact that in certain instances these structures may be the only ones giving clinical evidence of the presence of these diseases. SPAETH, Philadelphia.

NYSTAGMUS IN INFANTS. P. J. MOORAD, Arch. Ophth. **13**:238 (Feb.) 1935.

Moorad reports a case of the rare clinical condition monocular horizontal nystagmus. It is fairly well established that unilateral nystagmus without any demonstrable pathologic condition producing it is more likely to be vertical, rotary or mixed than horizontal. The ratio is about 1:4. The case reported was that of a child, aged 6 months. Nodding of the head started at the age of 2 months, and two months later the nodding stopped. The nystagmus, unilateral and horizontal, was very rapid—the author estimates about 250 oscillations per minute. The rate became more rapid a few seconds after lateral rotation. Intensity of light did not affect the motions of the eye, but nervousness seemed to increase the rate. Closing the right eye did not produce nystagmus in the left eye, and closing the left eye did not influence the character of the nystagmus in the right eye. After instillations of homatropine the nystagmus began to recede, and within a few days it had disappeared. SPAETH, Philadelphia.

TOXIC AMBLYOPIA DUE TO TOBACCO AND ALCOHOL. F. C. CORDES and DAVID O. HARRINGTON, Arch. Ophth. **13**:435 (March) 1935.

As early as 1896, de Schweinitz commented on the action exerted by strychnine, amyl nitrite and glyceryl tri-nitrate in cases of amblyopia arising from the use of tobacco. He stated that strychnine administered during the inflammatory stage of a lesion of the nerve tissue aggravates the disorder but that it is beneficial in cases of axial optic neuritis caused by tobacco poisoning. Some time later

Parsons agreed with Holden in thinking that the prime factor in the production of amblyopia due to tobacco was the vasoconstrictive action of the tobacco, mainly because of the already poor blood supply of the macular region, but that the secondary action was paralysis of the synapses of the cone fibers.

Eight cases are reported in detail. Vasodilating drugs only were used in treatment. In some of the cases the condition was well advanced. In every case there was much more rapid improvement of vision than would have been expected from withdrawal of tobacco alone. In some instances the amount of visual improvement was almost as remarkable as its rapidity. From a therapeutic standpoint, the results obtained from treatment with vasodilating drugs, e. g., sodium nitrite, seems to substantiate the argument that tobacco acts as a vasoconstrictor and that spasm of the retinal vessels is the primary etiologic factor in amblyopia due to tobacco or alcohol. For this reason the authors believe that vasodilating drugs deserve a definite place in the treatment of this condition.

SPAETH, Philadelphia.

DISPOSITION OF FIBERS OF RETINAL ORIGIN IN THE LATERAL GENICULATE BODY. RALPH W. BARRIS, Arch. Ophth. **14**:61 (July) 1935.

In this article the course and termination of fibers of the optic system in the brain of the cat are discussed. The manner of ending of crossed and uncrossed fibers of the optic tract in the lateral geniculate body has received comparatively little attention, although the projection of the various quadrants of the retina on the lateral geniculate body has been thoroughly investigated. Minkowski was the first to demonstrate that there is a separation of retinal fibers of crossed and uncrossed origin in the lateral geniculate body in a number of animals. Several weeks after removal of the eye in animals a chromatolytic degeneration of the cell bodies in certain cellular layers in the lateral geniculate body occurred. By comparing the appearance of the lateral geniculate bodies of the two sides, Minkowski was able to demonstrate that the fibers which remained uncrossed in the chiasm entered one set of cellular laminae and the fibers which crossed entered another.

Barris performed four series of experiments, each being designed to yield information relative to one or more of the constituents of the optic system. In the first series, one eye was removed from each of five cats and both eyes were removed from each of two cats. After from nine to eleven days the animals were killed and the mesencephalic and diencephalic regions of the brain studied. From the retinas of both eyes optic nerve fibers pass into the optic tract after partial decussation in the optic chiasm. Both crossed and uncrossed fibers establish connections with: (*a*) the dorsal nucleus of the lateral geniculate body; (*b*) the rostral part of the pretectal area, retinal fibers reaching this area by way of the brachium of the superior colliculus and the stratum zonale of the thalamus, and (*c*) the superior colliculus, retinal fibers reaching the dorsal portion of the stratum opticum by way of the brachium of the superior colliculus. No evidence was found for the termination of fibers of the optic tract in the ventral nucleus of the lateral geniculate body, the nucleus of the optic tract (nucleus lentiformis mesencephali), the pulvinar, the posterior part of the pulvinar or the nucleus of the posterior commissure. No fibers of retinal origin were found crossing in the posterior commissure or in the midline between the superior colliculi. The anterior and posterior accessory optic tracts could not be identified.

In the second set of experiments both eyes were removed from each of nine cats. After from six to eight months, during which time the primary optic fibers had undergone complete atrophy, a small lesion was placed in the dorsal nucleus of the lateral geniculate body in each animal. Barris believed that he was able thus to obtain secondary degeneration of fibers from the cells of origin in the lateral geniculate body and to determine whether fibers from this nucleus

passed to regions of the brain other than the visual cortex. The author found no evidence for the existence of geniculotectal, geniculopretectal, geniculopulvinar or geniculothalamic connections.

In the third set of experiments a portion of the right visual or striate area of the cerebral cortex was removed from each of six cats. This destroyed the cells of origin of some corticotectal fibers and of any other corticifugal fibers the cells of origin of which might lie within the circumference of the area in which the lesion was located.

In the fourth set of experiments a part of the right parastriate area was removed from each of three cats. The animals were killed after from nine to eleven days.

On the basis of the material obtained from the third and fourth set of experiments, Barris concludes that corticifugal fibers from the striate and parastriate areas of the cerebral cortex pass to the nucleus of the optic tract (nucleus lentiformis mesencephali), the ventral portion of the stratum opticum of the superior colliculus and the pontile nuclei by way of the transverse peduncular tract; that corticifugal fibers from the striate and parastriate areas do not terminate in the pulvinar, the posterior part of the pulvinar, the pretectal area, the posterior part of the lateral nucleus of the thalamus, the posterior thalamic nucleus or the dorsal and ventral nuclei of the lateral geniculate body.

An additional observation is that retinal impulses which pass to the cortex after passing through the geniculate body may also eventually reach the superior colliculus by way of corticifugal fibers. The functional significance of this is unknown.

SPAETH, Philadelphia.

THE CYTO-ARCHITECTONIC STRUCTURE OF THE OCCIPITAL LOBE IN MONKEYS (MACACUS RHESUS) AND IN MAN. EDUARD BECK, J. f. Psychol. u. Neurol. **46**:193, 1934.

According to Beck, most of the calcarine area in monkeys is not on the lateral surface of the occipital lobe but on its mesial surface, so that the dorsal limb of the calcarine fissure includes a considerable portion of the visual cortex, and the ventral operculum of the calcarine area is smaller than the dorsal operculum. There has apparently occurred considerable shifting of the calcarine area toward the mesial surface of the lobe, and although the ventral limb of the calcarine fissure is reached, the latter contains little visual cortex. In this respect the development of this part of the brain in monkeys assumes, to a certain extent, an intermediate position; "everything is still in a state of flux." This is also due to the fact that enormous portions of the calcarine area are still opercularized. Of special interest is also the fact that in spite of the opercularization of the ventral portion of the calcarine area the latter, owing to secondary gyrification, becomes unusually wide.

These findings assume new significance when one compares them with those in man, in whom this part of the brain is considerably more developed. In man the lateral portion of the calcarine area has regressed almost entirely; only in a small number of cases can the lateral surface be seen, and then it is found only in the caudal portion. In the human brain examined by Beck the lateral surface of the calcarine area extended only from the ventral limb of the calcarine fissure and reached caudally just about the lower margin of the lobe, somewhat to its outer surface. Whereas in monkeys the calcarine area is situated orocaudally in the dorsal limb of the calcarine fissure, or at most in its depth, in man it originates regularly in the ventral limb of that fissure, i. e., owing to shifting it has already reached the deepest point in the fissure. Obviously such differences in development must lead to corresponding differences in function.

Conditions are different on comparing the extrastriatal with the striatal portions of the occipital lobes in monkeys. Whereas the greatest part of the calcarine area is on the dorsal limb of the calcarine fissure, the greatest part of the extra-

striatal formation is on the ventral limb. An examination of the mesial surface of the occipital lobe with its unusually well developed gyrus lingualis and gyrus fusiformis leaves no doubt that the ventral portion of the occipital lobe is incomparably greater than the dorsal portion which extends to the gyrus transitorius cuneolimbicus and the cuneus anterior. These differences are still more striking on comparing the opercularization of the dorsal portions with that of the ventral. Here one finds on the ventral limb an unusually well developed secondary gyrification with extensive parastriatal formations, whereas on the dorsal limb only a small marginal border of the gyrus transitorius cuneolimbicus is included in the parastriatal formation. The ventral extrastriatal parts are unquestionably much more developed than the dorsal. This is true not only of the parastriatal formations but also of the entire occipital formation. The peculiar fineness and granulation of the parastriatal areas also seem to be of some functional significance in this portion of the occipital lobe.

The author states that he has not as yet studied the occipital lobe in man from this point of view.

KESCHNER, New York.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

May 24, 1935

FRANCIS C. GRANT, M.D., *Presiding*

CHRONIC SUBDURAL HEMATOMA: REPORT OF A CASE. DR. ROBERT A. GROFF.

This case is reported because of the confusing clinical and neurologic picture and also to call attention to the method of treatment instituted.

I. K., a white man, aged 50, was admitted to the service of Dr. A. Trasoff at the Mount Sinai Hospital on Feb. 12, 1935, with the complaint of severe headaches. He had been in good health until three months before admission, when he began to suffer from an intermittent dull aching pain in the small of the back. This increased when he assumed a standing posture. The pain continued for two weeks and then disappeared. The patient was free from pain until three weeks before admission to the hospital, when for no apparent reason a severe headache developed. The symptom originated in the occipital region and radiated over the entire head. At the onset it was intermittent, but in the course of two weeks it became constant and almost unbearable. The headache was sharp, and change of posture seemed to have no effect on it. It was at no time associated with nausea or vomiting. There were no further symptoms up to the time of admission.

The previous medical history did not reveal a severe or a mild injury to the head. The patient had been in the habit of consuming ½ ounce (15 cc.) of whisky daily for a number of years.

Physical examination at the time of his admission gave completely negative results. The patient showed a distinct tendency, because of the severe headaches, to lie quietly in bed. However, he was alert, responded to questions promptly and was oriented for both past and recent events. The left nasolabial fold was slightly flattened; otherwise neurologic examination gave negative results. Lumbar puncture yielded clear fluid under a normal pressure, 6 mm. of mercury. Examination revealed a normal amount of protein and 4 cells per cubic millimeter.

During the first week in the hospital the patient gradually became lethargic. He could be aroused without difficulty, but when he tried to be attentive he tired easily. Response to questions was rather slow. The answers were correct as far as they went. He was oriented for both past and recent events. There was distinct fluctuation from greater or lesser alertness to unresponsiveness.

Neurologic examination at this time revealed an oscillatory nystagmus on upward gaze. The right pupil was larger than the left, and the left eyelid drooped slightly. There was no motor weakness or sensory disturbance of the extremities. All abdominal reflexes were absent, except for a slight response in the left upper quadrant. There were bilateral ankle clonus and a positive extensor plantar reflex on the left. Plantar stimulation on the right produced a suggestive extensor reaction.

The impression formed was that the case was one of vascular disease, a tumor of the frontal lobe involving the corpus callosum or a chronic subdural hematoma, probably on the right side. The basis for this localization was the dilatation of the right pupil. An encephalogram was made. The initial pressure, with the patient in the sitting posture, was 270 mm. of water. One hundred cubic centimeters of fluid was removed, and a corresponding amount of air was injected. After the first 40 cc. had been removed the fluid became definitely yellow. Roentgenographic examination showed that the ventricular system had not been drained. A

small collection of air had accumulated along the tentorium and in the cisterna basalis. Because the results of the examination were inconclusive, both frontal lobes were exposed by trephination on February 25. Trephine openings were placed just at the hair line, 3 cm. lateral to the midline. The dura, as seen through the opening on the left side, appeared normal and was not under tension; the cortex beneath was normal.

The exposed dura on the right was white, thickened and under increased pressure. When it was opened there was a gush of fluid with a coffee-ground appearance. Approximately 50 or 60 cc. of this fluid was obtained. The cavity which had been formed by the pressure of the collection of fluid on the brain was irrigated with physiologic solution of sodium chloride through the opening until the fluid returned clear. Force was used in this maneuver in order to break up adhesions. The opening on the right side was closed with interrupted silk sutures without drainage, and that on the left was closed in like manner after a small piece of rubber tissue had been inserted for drainage.

Almost immediately after the release of degenerated blood and the lowering of the intracranial tension, the patient's condition improved. In several days the mental picture was entirely normal, and all neurologic signs had disappeared. The patient was discharged from the hospital fourteen days after operation.

The diagnosis in this case was difficult. The initial symptom of pain in the small of the back seemed to have no relationship to the more recent complaint of severe headache. Because there was no history of injury to the head, either mild or severe, tumor or vascular disease was considered more probable than chronic subdural hematoma. It was not until exploratory perforations over the frontal lobes were made that the diagnosis was established.

The clinical picture was characterized by gradually increasing headache for three weeks, with a rapid development of increasing somnolence and of neurologic signs during the fourth week. This represents a fairly typical story of a patient with a chronic subdural hematoma, though longer and shorter courses have been recorded. The generally increased reflexes, the absence of abdominal reflexes, and the presence of ankle clonus and bilateral extensor plantar reflex were not of localizing value. These signs varied with each examination, but dilatation of the pupil was present constantly on the right side. The sign occurred on the side of the lesion, and, as pointed out by Kaplan (*Brain* **51**:430, 1931), it is of distinct localizing value. The fact that it was present together with a more definite Babinski sign on the left side favored the diagnosis of a lesion on the right side. Grant (*Ann. Surg.* **86**:485, 1927) and Trotter (*Brit. J. Surg.* **2**:277, 1914) have emphasized the variability of signs, and the latter stated that a Babinski sign and reduction or loss of abdominal reflexes are the most valuable signs.

The method of treatment utilized in this case was first described by Fleming and Jones (*Surg., Gynec. & Obst.* **54**:81, 1932). The procedure consists in making two trephine openings over the hematoma and evacuating the blood by means of through and through irrigation. Frazier (*Ann. Surg.* **99**:671, 1934) considered this the method of choice and stated that it offers the advantages of localization of the hematoma with the minimum risk and evacuation of bilateral clots at one sitting. To this I wish to add that the postoperative convalescence is much smoother, and the patient is left without a cranial defect. This method, however, is suitable only for hematomas which have liquefied. For others a cranioplastic flap is necessary.

DISCUSSION

DR. F. C. GRANT: I felt much less optimistic about this case as far as diagnosis was concerned than did Dr. Groff. When I saw the patient at the University Hospital, I had the impression that he had arteriosclerosis, with probably senile mental changes; in order to elucidate that diagnosis it was suggested that an encephalogram be made. The ventricles failed to fill, and my experience is that when this occurs it is fairly good evidence that there is a gross lesion. This result focused attention on the few lateralizing signs and suggested the possibility of a chronic subdural hemorrhage. One of the reasons for arriving at

this particular diagnosis was that there had been periods of remission and an increase in the symptoms. The patient would be bright on one occasion and dull on others.

As far as the operative procedure outlined by Dr. Groff is concerned, I think that trephination should be used as an initial procedure. I prefer two openings to one. I think that Dr. Groff was fortunate in accomplishing his purpose in this case through a single opening. If this procedure does not work, or if one finds a solid clot which cannot be evacuated through the opening, an osteoplastic flap is necessary. At times in these cases, however, evacuation of the blood is not followed by expansion of the brain.

Dr. S. N. Rowe: I wonder why many of these patients show evidence of injury of the third nerve, a difference in the size of the pupils and perhaps sometimes a little ptosis. Most of the hematomas I have seen were situated over the vertex rather than around the base, so that it is difficult to understand the reason for the pupillary differences.

Dr. R. A. Groff: I cannot say as to the exact cause of the dilatation of the pupil, but it occurs in a good percentage of cases.

Myotonia Acquisita: A Case in Which Myotonia Was Present in Both Limbs After Injury. Dr. Matthew T. Moore.

This patient presents certain characteristics which conform to the concept of a myotonic syndrome. The myotonic disorder of movement is manifested by marked difficulty in relaxation of the muscles of the lower limbs, slowness in initiation of movements, particularly in arising and in walking, and spasm of the gastrocnemius muscles when they are brought into play. The myotonic reaction to mechanical and electrical stimuli is not fully present. There is a delayed and considerably diminished response to both faradism and galvanism. Erb's phenomenon is simulated by an undulating response of the gastrocnemius muscle to a strong faradic current.

Hypertrophy, which according to Krabbe accounts for much of the myotonic phenomena, is evident to a marked degree. The right calf shows the hypertrophy somewhat more than the left; both calves feel extremely hard, even when relaxed. They do not have the distinctive feel of the muscle of the calves of a patient with pseudohypertrophic muscular dystrophy but are much like the well developed muscles of an athlete.

The etiologic factor was unquestionably trauma. A review of the literature reveals only 3 cases of myotonia acquisita occurring after direct injury to a part. Jacoby described the case of a pianist, aged 40, who fell, striking the palms of both hands. This was followed immediately by pain and swelling of the wrists, which subsided within ten days. Shortly thereafter he was compelled to give up his profession because of cramps in the fingers and stiffness of the arms. Within six months the arms, shoulders and neck showed marked muscular hypertrophy and the symptom of myotonia. The muscle groups of the rest of the body were not involved. In Lhermitte's case, that of a soldier aged 25, myotonia occurred after injury of the sciatic nerve by a bullet. The hypertrophy and myotonia were accompanied by persistent pain in the distribution of the injured nerve. Rimbaud and Jourdan reported a case (in which they termed the condition Thomsen's disease because of the myotonia) of a gardener, aged 28, who had myotonia of the limbs following direct injury to them. This was obviously an acquired myotonia and not the hereditary type of Thomsen.

The pain and areas of paresthesia were in all probability due to a posttraumatic neuritis. Krabbe, in summarizing his cases of myotonia acquisita, stressed the presence of neuritis or polyneuritis in the majority of them.

Hypertrophy of muscle following an injury is not readily explainable. Ordinarily some degree of atrophy follows injury to a muscle, particularly if the nerve supplying it is injured. Accompanying the atrophy are muscular weakness, flaccidity and some vasomotor phenomena. The contention that neuritis preceding the hypertrophy may have stimulated the elements of the muscle tissue to growth

is somewhat conjectural and not definitely established as fact. Lhermitte raised the question whether the enlarged muscles represent true hypertrophy or merely a proliferative myositis with interstitial elements producing the apparent hypertrophy.

ACUTE DISSEMINATED ENCEPHALOMYELITIS. DR. FREDERIC LEAVITT.

A girl, aged 11 years, had an acute febrile condition diagnosed as chickenpox in the summer of 1933. She made an uneventful recovery from this illness. About September 1933 she complained of being unable to see the writing on the blackboard and the print in her books. At this time she had headache. She could not think properly, and it was noticed by teachers that at times she seemed dazed and confused. Often she exhibited peculiar behavior, such as trying to get into her clothing wrong side out. On examination in November 1933 she had a very vacant expression, a lack of blinking of the eyelids, slowness of movement and monotonous speech. The pupils were dilated and reacted well. Ophthalmoscopic examination revealed nothing abnormal. Laboratory studies gave negative results.

The condition progressed gradually, and in the course of three or four months the patient became blind. Nothing was found in the eyegrounds to account for the blindness. She then became progressively deaf, and finally there developed a marked type of decerebrate rigidity, with atypical chronic convulsions. Finally the child became completely unconscious, without exhibiting signs of increased cranial pressure.

The pathologic diagnosis made by Dr. B. J. Alpers was disseminated encephalomyelitis, with numerous foci of infiltration and demyelinization in the brain stem and cortex.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

Sept. 19, 1935

ALBERT M. BARRETT, M.D., *in the Chair*

INTERPRETATION OF ENCEPHALOGRAMS. DR. RUSSELL N. DEJONG and DR. R. W. WAGGONER.

Since its development by Dandy in 1919, encephalography has become an important diagnostic procedure in neurologic and neurosurgical clinics. Over 150 encephalograms were made at the University Hospital during the past year. We believe that encephalography is a better routine procedure than the direct injection of air into the ventricles, as it results in better delineation of the intracranial structures. Ventriculography, a relatively major surgical procedure, is reserved for cases in which there is increased intracranial pressure. In order more effectively to correlate encephalographic findings with abnormalities in the structure of the brain, a few cases are presented in which it was possible to compare the picture seen in the encephalogram with the results of postmortem examination of the brain.

CEREBRAL PATHOLOGIC PICTURE IN TWO CASES IN WHICH DEATH OCCURRED AFTER THE ADMINISTRATION OF NITROUS OXIDE AND OXYGEN. DR. K. LÖWENBERG, Ann Arbor, Mich.

CASE 1.—A white man, aged 22, was operated on for a purulent infection and swelling of the second right metacarpal bone. Twenty minutes after the administration of the anesthetic was begun, respiration suddenly ceased. Oxygen was administered, and respiration was established ten minutes later. The patient was

rigid and remained unconscious. The rectal temperature rose to 108 F.; the pulse rate varied from 120 to 160. The patient died without regaining consciousness approximately sixty hours after the operation. Histopathologic examination of the brain disclosed an extremely severe degeneration of the gray matter of both hemispheres and extensive degeneration of the basal ganglia and of the brain stem.

CASE 2.—W. G., aged 28, was operated on for chronic appendicitis. Respiration ceased suddenly approximately thirty minutes after the initiation of anesthesia and was restored forty minutes later. Spasticity of the extremities developed, and the patient remained unconscious. The temperature rose to 106 F. and the pulse rate to 160. The patient died without regaining consciousness approximately seventy-two hours after the operation. Histologic examination revealed severe degeneration of the gray matter of the cerebral hemispheres and extensive degenerative lesions in the basal ganglia and in the brain stem.

The histologic picture was identical in the two cases, the cortex showing the most severe damage. The histologic picture was purely degenerative in type and of recent origin.

In a third case, that of a white woman aged 29, operation was performed for closure of a fistula following an abscess of the lung. There were no disturbances during the period of anesthesia. The patient became restless in the afternoon, approximately four hours after the operation, and was partly unconscious for the following three days. Severe mental confusion and paralysis of the right side developed. After a protracted illness the patient made an incomplete recovery. When she was seen five years later there was a suggestion of palsy on the left side of the face, and she had a slightly spastic, ataxic gait.

A review of the literature revealed 26 cases in which death occurred either suddenly or several hours, days or weeks after the administration of an anesthetic. In analyzing the histologic changes, I conclude that the fatal outcome is due not to anoxemia but to the gas itself.

SCHIZOMANIA: REPORT OF A CASE. DR. ALBERT M. BARRETT.

The patient, aged 18, comes of a family in which two members are epileptic. At about the age of 8 he presented a difficult problem in the family because of stubbornness and resistance to parental training. His affective reactions in family and social relationships were contrasting; sometimes he was affectionate and considerate, but more often he was antagonistic and self-willed. As he grew older he became egocentric and finicky in his tastes, and his behavior was sometimes of a compulsive type. During the past year his interests have become somewhat narcissistic, and his reading has dealt much with physical health and psychologic topics. At about the age of 14 he was involved in a homosexual experience with a Sunday school teacher. He became bitter against churches and religious teachings. At 16 he secretly married a girl somewhat younger than himself. Family objections to this led to annulment of the marriage. Afterward his thoughts dwelt much on his former wife, and for a few weeks he was rather severely depressed. There then developed abruptly a phase of excitement, in which he was overactive and distractible and showed a pressure of thought with expansive ideas, many of which were of mystical content, such as "You are the Father, I am the Son, but who is the Holy Ghost?" He spoke of his sexual organs as being nature pressing down on him. Eight weeks after the beginning of the period of excitement he came to the hospital.

In somatic structure he is of extreme asthenic build. There is no somatic or neurologic abnormality. Since he has been under observation his reactions have been dominantly manic, but usually there are also many of the reactions met with in cases of schizophrenia. His motor reactions are springy in occurrence, impulsive and often stereotyped and manneristic. During the first month in the hospital he was quiet and semistuporous at times, and then suddenly he would burst into a state of violent excitement. On some days there were contrasting

fluctuations in the affective field: A period of crying would be abruptly followed by a period of boisterous euphoric excitement. A month after admission the degree of excitement lessened. From the time he entered the hospital there was a steady increase in weight, and now he is 15 pounds (6.8 Kg.) heavier. He is amnesic to much that occurred during this period of excitement. The period of quietude was followed suddenly by a brief period of excitement. During this he was tormented by vivid auditory hallucinations which influenced his behavior. There then occurred a severe epileptiform convulsion, with tonic and clonic movements, followed by deep coma. After this there was another episode of typical manic excitement, which lasted about a week. As this passed away the patient gradually became more quiet and accessible and has continued so until now. While the more violent aspects of his disorder have passed away, there persists a definite oddity of behavior with mild dulling of affect and at times attitudes such as those observed in terminal states of schizophrenia.

Clinical disorders of the type presented by this patient are not uncommon and have come to be called schizomanic states. The problems of diagnosis in cases of states of this type are of more than theoretical interest, as a proper evaluation of the factors present bears directly on the prognosis. They require a deeper insight into both manic-depressive and schizophrenic mechanisms. While knowledge of the pathologic processes underlying the disorders is vague, one sees both constitutional factors and those of experiences. Each disease seems to have its specific qualities, but the mechanisms of the two may intermingle to produce confusing clinical pictures.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 17, 1935

S. W. Ranson, M.D., *President, in the Chair*

Report of the Second International Neurological Congress, London, England, July 29 to Aug. 2, 1935. Dr. Leroy H. Sloan and Dr. Theodore T. Stone.

Areas 4 and 6 of the Cerebral Cortex and Their Projection Systems. Dr. Paul C. Bucy.

Recent investigations, both anatomic and physiologic, necessitate a reconsideration of the functional activity of the precentral excitable cortex.

Anatomic Considerations.—The division of the precentral region into the cytoarchitectonic areas 4 and 6 of Brodmann has served a useful purpose in the clarification of the functional activity of this portion of the cerebral cortex, but it has also obscured certain facts in that there is a tendency for these two areas to be looked on as more or less different and independent cortical fields. Area 4 has come to be identified solely with the corticospinal fibers, the pyramidal tract. Area 6 has been looked on as the point of origin of those motor projection fibers other than the pyramidal fibers which arise in the precentral area. Although there is a certain measure of truth in this theory, it falls far short of complete accuracy. Knowledge of the structure and function of the precentral region has now reached the point where a more comprehensive and accurate conception of this area is regarded as essential. As will be pointed out, consideration of the pyramidal system and of that more complex group of efferent projection fibers other than pyramidal fibers which arise from the precentral region and which at the suggestion of Dr. Stephen Poljak are here referred to as the parapyramidal system is preferable to a consideration of areas 4 and 6 as functional units. (The term parapyramidal has been used to designate the efferent pathways

which arise from the precentral region (areas 4 and 6) other than the true pyramidal tract, which arises from the gigantic cells of Betz. The term extrapyramidal has been used by some authors in this connection. It has been avoided here because previous usage has assigned to it various other connotations. Jakob used the term extrapyramidal to designate the subcortical nuclei (basal ganglia, etc.) and their fiber connections. Foerster has recently designated numerous cortical areas [areas 6a, 1, 2, 3, 5, 7b and 22] other than area 4 which he considered to be part of the cortical mechanism controlling skeletal movement as the extrapyramidal motor cortical fields.)

It has been repeatedly pointed out that areas 4 and 6 are nearly identical microscopically, except for the presence of the gigantic pyramidal cells of Betz in area 4. It would appear likely, then, that this region is composed of two distinct, though not independent, systems, the pyramidal and parapyramidal efferent projection systems of the precentral region. These two systems are not strictly and exclusively confined to any cyto-architectonic topographic division of the precentral cortex. It is true that by definition the Betz cells are limited to area 4 of Brodmann. If, as Holmes and May showed and Levin and Poljak recently confirmed, the pyramidal tract (corticospinal fiber system) arises exclusively from the cells of Betz, it is apparent that the pyramidal system is coextensive with area 4. But the pyramidal fibers are not the only ones which arise from this cyto-architectonic area. As Levin and Poljak have shown clearly, the fiber projection systems of areas 4 and 6 are identical from a purely morphologic standpoint except that the corticospinal fibers arise almost solely from the Betz cells of area 4 and the parapyramidal fibers arising from area 4 are more numerous than those arising from area 6 in the monkey, being at the same time more numerous than the pyramidal fibers themselves. Thus one may look on the pyramidal system as being represented solely by area 4, and on the parapyramidal system, composed of fibers connecting the cortex with subcortical centers within the basal nuclei and the brain stem, as being represented by both areas 4 and 6. In other words, there are two closely related systems, pyramidal and parapyramidal, the latter being more extensive and overlapping the former. In some species this overlap is more complete than in others, and, as has been recently pointed out (Bucy), the overlap seems more nearly complete in the carnivora than in the primates. Certainly from a purely topographic standpoint the overlap is greater in the common rhesus monkey (Macaca mulatta) than in the chimpanzee or orang-utan and definitely less in man than in the ape. In other words, as the phylogenetic scale is ascended the pyramidal and the parapyramidal system tend to become more and more separated, the pyramidal system occupying the posterior part of the precentral region and the parapyramidal system shifting progressively anteriorly. Thus, area 4 is more exclusively identified with the pyramidal system in man than in the ape or the monkey. However, even in man, though the morphologic separation of the two systems is greater than in the subhuman primates, it is not complete.

Physiologic Consideration.—The relative importance of the cortical motor projection systems varies greatly in different species. Thus, in the carnivora, for instance the dog and the cat, the sigmoid gyrus, from which these projection systems arise, or even the entire cortex may be removed without seriously interfering with the integration of motor activities. In the monkey, although unilateral removal of the precentral cortex, both area 4 and area 6, results in temporary hemiplegia, motor activity almost comparable to that seen in the intact animal soon returns. However, quite unlike the results seen in the carnivora, bilateral extirpation in the monkey of the cortical representation of the motor projection systems (areas 4 and 6) produces permanent and total disability, only a few subcortical reflexes remaining. In the ape the deficit following a unilateral lesion is somewhat greater and more lasting than in the monkey. In man a unilateral lesion of the cortical efferent systems results in permanent, if not complete, paralysis, as illustrated by ordinary spastic hemiplegia or by the results in a few cases after extensive extirpation of a hemisphere The arm is more completely

paralyzed, whereas voluntary movements of the lower extremity, though seriously impaired, are less involved, and walking is usually possible. It is thus apparent that as the phylogenetic scale is ascended the cortical motor projection systems achieve more and more significance and that damage to these systems is attended with greater deficit in the higher forms than in the lower. It is also worthy of note that these functional differences are not associated with apparent morphologic differences of as great a degree.

Originally Fulton and his co-workers pointed out that there is an essential difference between the condition which results in the monkey from the unilateral extirpation of area 4 and the unilateral removal of areas 4 and 6. The paralysis which results from removal of area 4 is more flaccid than that which follows the more extensive extirpation. They thus concluded that destruction of the pyramidal tract results in flaccid paralysis, that the parapyramidal systems arising from area 6 inhibit the subcortical reflexes which give rise to spasticity and that the fibers from area 6 must be destroyed in order that the paralysis become spastic. The original observations were made on the rhesus monkey (Macaca mulatta) and have been seriously questioned by some neurologists (Walshe). This is not surprising. The difference between the conditions which result from lesions of area 4 and of areas 4 and 6 in the monkey are not great, and it is a tribute to the keenness of Fulton's observations that he noted it. When the experiments were extended to the ape, however, there could be no question of the accuracy of the observation. No one who has seen a chimpanzee with the "arm" area of area 4 removed from one hemisphere and the "arm" area of area 4 and that portion of area 6 lying immediately anterior to it removed from the opposite hemisphere could doubt this fundamental point. Several such animals were prepared by Fulton and his associates. The upper extremity opposite the hemisphere in which area 4 alone has been damaged hangs limply at the animal's side, while the other upper extremity is held in a rigidly flexed position not unlike the position of the involved arm in a hemiplegic human being. One might rightfully ask the reason for this great difference between the ape and the monkey, which was pointed out in one of the earliest papers from Fulton's laboratory. The reasons seem fairly apparent and are at least twofold. First, there is the demonstrably greater influence of the cortical motor systems in the ape. Thus, in that species the paralysis is more enduring, the spasticity is more marked and differences between the flaccid and the spastic extremities are more clearly seen. But that is not all. As I have previously pointed out, the pyramidal and parapyramidal systems are more nearly coextensive in the monkey than in the ape; i. e., the pyramidal system is overlaid by more of the parapyramidal system in the monkey than in the ape. Extirpation of area 4 in the monkey destroys all of the pyramidal system as it does in the ape, but it also destroys considerably more of the parapyramidal system than in the ape. In other words, a lesion involving area 4 in the chimpanzee is more nearly exclusively a lesion of the pyramidal system than in the monkey. It is not surprising, then, that the difference between a lesion of area 4 and one of areas 4 and 6 is greater in the ape than in the monkey.

If it is correct, as Levin and Poljak have shown, that the origin of the parapyramidal cortical projection system is coextensive with areas 4 and 6 and that this parapyramidal system is responsible for the inhibition of the reflexes (stretch reflex, etc.) which give rise to spasticity, then a destructive lesion of area 4, although giving rise to a relatively flaccid paralysis (as compared with that arising as a result of destruction of areas 4 and 6), should present some evidence of spasticity because part of the parapyramidal system as well as part of the pyramidal tract is destroyed. And that is exactly what happens. To quote from a recent statement by Fulton "complete experimental ablation of area 4 causes transient paralysis, transient depression of reflexes and transient flaccidity. In the stages of recovery from a lesion of area 4 deep reflexes may become moderately hyperactive but gross spasticity has never been observed. . . ." Elsewhere throughout the papers in which the experiments performed in Fulton's laboratories are reported in detail the same fact is evident.

Furthermore, a destructive lesion of area 4 should, for the same reason, give rise to greater spasticity than a lesion of the pyramidal tract alone, which theoretically should give rise to purely flaccid paralysis. At the moment no critical observations on this have been made in primates, but an excellent demonstration of this point has been conducted by Tower in cats. In the state resulting from a unilateral transection of the pyramidal tract in the bulb there is a "conspicuous absence of all signs of spasticity" and of any "evidence of release of any lower mechanism." However, on removal of the contralateral "motor cortex" there appeared "definite rigidity in the affected legs as a new contribution to the syndrome." In these experiments there would seem to be no doubt but that destruction of the parapyramidal (noncorticospinal) fibers arising from the motor cortex gave rise to the spasticity. Furthermore, stimulation of the motor cortex on the side opposite that on which the pyramidal tract had been severed gave rise to "relaxation of the extensor tonus" induced by light ether anesthesia, which numerous investigators have compared to decerebrate rigidity. These experiments leave little doubt that the parapyramidal system arising from the motor cortex inhibits the subcortical reflexes, which give rise to extensor rigidity, and that destruction of this system changes the flaccid paralysis which results from an exclusive lesion of the pyramidal tract into spastic paralysis.

In this brief note all reference to the relationship of the parapyramidal system to various visceral, vasomotor and other "sympathetic" activities has been intentionally omitted.

DISCUSSION

DR. PERCIVAL BAILEY: I wish to ask Dr. Bucy whether he knows of any cases in which flaccid paralysis in man due to purely spinal lesions remained flaccid.

DR. S. W. RANSON: As I remember Dr. Margaret Kennard's paper, these fibers from the premotor cortex pass downward through the pyramidal tracts. If so, resection of the pyramidal tracts, according to Dr. Bucy's thesis, should produce rigidity. I wish also to call attention to Dr. Sarah Tower's findings in regard to paralysis following section of the pyramidal tracts in the medulla. Dr. Bucy indicated that when animals were properly supported ventral side down the limbs were held extended. Tower had stated, however, that this was due to absence of flexion and not to an extensor rigidity. However, Marshall, of Yale, who had done the same work previously, found an increased resistance to flexion following section of the pyramidal tracts. That has been my experience in the acute experiments in which I exposed the medulla by making an opening in the occipital bone through the mouth, cutting the pyramidal tracts. These animals had something more than an absence of flexion. There was real extensor rigidity, and when the section was unilateral the rigidity was contralateral. Whether the rigidity which follows section of the pyramidal tracts is due to division of fibers from the motor cortex proper or to division of fibers from the premotor cortex is an entirely different matter.

DR. RALPH W. GERARD: Did Dusser de Barenne report any differences in tonus in animals subjected to destruction of the laminae of the motor cortex by his thermocoagulation method? This also should be a means of separating the true motor effect of the pyramidal tracts from parapyramidal tonus by destroying the cortex to or through the Betz layer.

DR. PAUL C. BUCY: So far as I am aware, there is nothing in Dusser de Barenne's experiments on thermocoagulation of the cortex which deals specifically with this problem. He has shown that after destruction of the first three layers of the cortex of area 4, leaving the fifth layer, the Betz cell layer, intact, electrical stimulation gives rise to movements comparable to those elicited from the intact area 4.

I know of no cases of permanent flaccid paralysis occurring in man as a result of a spinal lesion except cases of so-called "spinal shock" from sudden transection

of the spinal cord. Here, it will be generally conceded, one is dealing with another problem. Flaccid paralysis from cortical lesions is, of course, not uncommon.

In this paper and in the discussion, consideration of the work of Kennard (ARCH. NEUROL. & PSYCHIAT. **33**:698 [April] 1935) and Hoff (ibid. **33**:687 [April] 1935) has been avoided, as the question of the origin of any corticospinal fibers arising from area 6 is at the moment being reinvestigated in the laboratories of the division of neurology and neurosurgery of the University of Chicago. Recent work by Levin (*J. Comp. Neurol.,* to be published) does not support their findings.

It is, of course, entirely possible that Tower's observations are incorrect. Having had no personal experience with this particular phase of the problem, it is impossible for me to criticize her work as Dr. Ranson is able to do. It should be borne in mind, however, that although on purely theoretical grounds a lesion restricted to the pyramidal tract may give rise to purely flaccid paralysis, more extensive lesions of the brain stem in this general region may give rise to spastic paralysis. It is thus of utmost importance that the exact extent of the lesion in any given case be known. The ultimate conclusion as to whether the paralysis which results from a lesion of the pyramidal tract is spastic or flaccid does not necessarily militate against the consideration of the pyramidal and parapyramidal systems as expressed in this brief note, as the nature of the entire nerve fiber composition of the pyramidal tracts is at the moment unknown. The pyramidal tracts may contain fiber systems other than those arising from the cortex which are capable of inhibiting the postural reflexes.

HEAT REGULATION IN CHRONIC ENCEPHALITIS. DR. ISIDORE FINKELMAN and DR. W. MARY STEPHENS.

This article will be published in full in a later issue of the ARCHIVES.

Book Reviews

Textbook of Abnormal Psychology. By Roy M. Dorcus and Wilson G. Shaffer. Price, $4. Pp. 389, with illustrations. Baltimore: Williams & Wilkins Company, 1934.

When a physician picks up this book his first query might naturally be: "What need is there for a study of abnormal psychology? Why cannot a psychologist study 'psychiatry' in one of the many good textbooks on that subject?" The authors have partly answered this in their preface by stating: "This text has been written to fill the needs of advanced students in Psychology, Pre-medical students and Medical students who desire more psychological information. The facts and principles of abnormal psychology have been presented by other texts almost entirely apart from the principles of normal psychology. In the present text, the authors have attempted to approach the discussion of abnormal phenomena through consideration of the normal. The symptoms and behavior of the abnormal individuals are not seen as completely new or mysterious ways of reacting but are recognized as exaggerated manifestations of normal functioning. Thus, dissociations of the personality are viewed in the light of the various conceptions of normal integration; and the abnormalities in the attempts at satisfaction of desires are considered through an understanding of the normal functioning of desires."

The field and scope of abnormal psychology is apparently difficult to define. A whole chapter is devoted to this discussion, which boils down to the facts that "normal" means "average" and that abnormal psychology concerns itself with "unusual mental activity," e. g., "An individual with an exceptionally keen memory, or one with hyper-tactual sensitivity, or an expert wine taster must be considered as belonging to an abnormal class of individuals. It is just as much a problem for the abnormal psychologist to formulate theories and rules for the origin and development of geniuses as it is his problem to explain the genesis of personality disorders. In other words, the extremes or deviations from the average, regardless of whether above or below, are of interest to our discussion." This at last brings out a differentiation from psychiatry. It is a good idea, but it is not lived up to in the book, for one looks almost in vain for a discussion of exceptional ability, experts and geniuses in the text, while there is a great deal about mental disorder.

The first hundred pages give a good summary of neuropathology, with a smattering of anatomy and clinical neurology. The psychologic emphasis is well sustained. The next hundred pages are the best, containing discussions of mechanisms, feelings, emotions, sleep and dreams; this material summarizes for most physicians new and important points of view. The authors are fair to a fault; they review many theories, often too many, for some of them are not worth discussing.

The last hundred and sixty-five pages of the book comprise a somewhat inadequate textbook of psychiatry. Paranoia is especially well discussed. The manic-depressive psychosis is given a biased exposition, in which the important facts of heredity are briefly passed over and the psychogenic aspects are overemphasized. The psychoneuroses are reasonably treated, but epilepsy is classed with them. The section on "the epilepsies" is the worst in the book; there is no grasp of the problem, and such outworn conceptions are brought up as "genuine epilepsy," "true seizure" and "epileptic personality." This is the kind of exposition that might be expected of authors who read and abstract much literature but have little clinical experience.

Modern Problems in Schizophrenia. Price, 3.50 roubles. Pp. 166. Moscow, U. S. S. R.: State Publishing Company, 1933.

This volume contains a collection of papers read at the conference on schizophrenia in Moscow in the summer of 1932 under the auspices of the Moscow Psychiatric Society and the Communistic Academy of Sciences. In spite of the marked domination of Russian psychiatry by German nosologic influences, one can see a great deal of independence, with definite attempts to get away from the heavy formalistic point of view.

In the introductory paper by Vnukoff it is pointed out that under the influence of some hypothetical toxins the whole personality of the patient changes, especially in the relationship to the outside world. Differentiation of the individual from the group and the relationship of the individual to the group is an evolutionary faculty which develops late. It is this function which is especially disturbed in schizophrenia, so that the patient never knows his exact relationship to the world outside him. The whole treatment of schizophrenia as a personality disorder is evidence of a gradual penetration of Russian psychiatry with a more dynamic point of view.

Vigotsky in a paper on the psychology of schizophrenia points out that in this disease there is a disturbance in the faculty of concept formations, as evidenced by his experimental work. In schizophrenia thinking is reduced to the more simple forms which is characteristic of children and primitive races. He expresses the same ideas as were stated in his paper published in English ("Thought in Schizophrenia," ARCHIVES OF NEUROLOGY AND PSYCHIATRY **31**:1063 [May] 1934).

Serejsky in a paper on the biologic problems of schizophrenia states that there is a definite defect in the lipoid substances in the brain and raises the question of feeding schizophrenic patients with cerebral lipoids. There is an interesting paper by Chlenov and Popova on the neurology of schizophrenia. These authors point out that nystagmus occurs in 18 per cent of the cases, and that these are hippus, and decreased motility of the eyeball, with a tendency toward staring, which gives the eyes a bright, shiny appearance. The abdominal and cremasteric reflexes are usually decreased. There are also increased secretion of the sebaceous glands, which gives an oily appearance to the face; cyanosis of the extremities, and increased perspiration, although certain parts of the body remain unusually dry. The schizophrenic patient often holds his forearm in a special position which closely resembles a thalamic position. They think that these findings are more in the nature of symptoms pointing to diffuse involvement of the nervous system rather than so-called "stigmas."

There are two papers on schizophrenia in children, with emphasis on the regressive phenomena of children which are similar to those in adults. Unfortunately, the problem of schizophrenia in children is dealt with from a purely symptomatic point of view, without any attempt to understand the dynamics of the disease.

Rosenstein, the late director of the Russian Society for Mental Hygiene, reports several instances of mild schizophrenia, which he describes as the "soft forms of schizophrenia." These forms correspond with American ideas of mild psychotic episodes in schizoid personalities.

Other papers deal with occupational therapy in and the medical aspects of schizophrenia. The volume shows the competence and vigor with which Russian psychiatrists are attacking the difficult problem of schizophrenia.

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